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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/34, 31/38, 31/40

A1

(11) International Publication Number: WO 98/52558

(43) International Publication Date: 26 November 1998 (26.11.98)

(21) International Application Number: PCT/US98/10375

(22) International Filing Date: 21 May 1998 (21.05.98)

(30) Priority Data:
08/863,022 23 May 1997 (23.05.97) US

(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application
US 08/863,022 (CIP)
Filed on 23 May 1997 (23.05.97)

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: INHIBITION OF p38 KINASE ACTIVITY BY ARYL UREAS

(57) Abstract

This invention relates to the use of a group of aryl ureas in treating cytokine mediated diseases other than cancer and proteolytic enzyme mediated diseases other than cancer, and pharmaceutical compositions for use in such therapy.

Inhibition of p38 Kinase Activity by Aryl Ureas

Field of the Invention

This invention relates to the use of a group of aryl ureas in treating cytokine mediated diseases and proteolytic enzyme mediated diseases, and pharmaceutical compositions for use in such therapy.

Background of the Invention

Two classes of effector molecules which are critical for the progression of rheumatoid arthritis are pro-inflammatory cytokines and tissue degrading proteases. Recently, a family of kinases was described which is instrumental in controlling the transcription and translation of the structural genes coding for these effector molecules.

The MAP kinase family is made up of a series of structurally related proline-directed serine/threonine kinases which are activated either by growth factors (such as EGF) and phorbol esters (ERK), or by IL-1, TNFα or stress (p38, JNK). The MAP kinases are responsible for the activation of a wide variety ~~of~~ transcription factors and proteins involved in transcriptional control of cytokine production. A pair of novel protein

kinases involved in the regulation of cytokine synthesis was recently described by a group from SmithKline Beecham (Lee et al. *Nature* **1994**, *372*, 739). These enzymes were isolated based on their affinity to bond to a class of compounds, named CSAIDs (cytokine suppressive anti-inflammatory drugs) by SKB. The CSAIDs, pyridinyl imidazoles, have been shown to have cytokine inhibitory activity both *in vitro* and *in vivo*. The isolated enzymes, CSBP-1 and -2 (CSAID binding protein 1 and 2) have been cloned and expressed. A murine homologue for CSBP-2, p38, has also been reported (Han et al. *Science* **1994**, *265*, 808).

Early studies suggested that CSAIDs function by interfering with m-RNA translational events during cytokine biosynthesis. Inhibition of p38 has been shown to inhibit both cytokine production (eg., TNFα, IL-1, IL-6, IL-8; Lee et al. *N.Y. Acad. Sci.* **1993**, *696*, 149) and proteolytic enzyme production (eg., MMP-1, MMP-3; Ridley et al. *J. Immunol.* **1997**, *158*, 3165) *in vitro* and/or *in vivo*.

Clinical studies have linked TNFα production and/or signaling to a number of diseases including rheumatoid arthritis (Maini. *J. Royal Coll. Physicians London* **1996**, *30*, 344). In addition, excessive levels of TNFα have been implicated in a wide variety of inflammatory and/or immunomodulatory diseases, including acute rheumatic fever (Yegin et al. *Lancet* **1997**, *349*, 170), bone resorption (Pacifici et al. *J. Clin. Endocrinol. Metabol.* **1997**, *82*, 29), postmenopausal osteoporosis (Pacifici et al. *J. Bone Mineral Res.* **1996**, *11*, 1043), sepsis (Blackwell et al. *Br. J. Anaesth.* **1996**, *77*, 110), gram negative sepsis (Debets et al. *Prog. Clin. Biol. Res.* **1989**, *308*, 463), septic shock (Tracey et al. *Nature* **1987**, *330*, 662; Girardin et al. *New England J. Med.* **1988**, *319*, 397), endotoxic shock (Beutler et al. *Science* **1985**, *229*, 869; Ashkenasi et al. *Proc. Nat'l. Acad. Sci. USA* **1991**, *88*, 10535), toxic shock syndrome (Saha et al. *J. Immunol.* **1996**, *157*, 3869; Lina et al. *FEMS Immunol. Med. Microbiol.* **1996**, *13*, 81), systemic inflammatory response syndrome (Anon. *Crit. Care Med.* **1992**, *20*, 864), inflammatory bowel diseases (Stokkers et al. *J. Inflamm.* **1995-6**, *47*, 97) including Crohn's disease (van Deventer et al. *Aliment. Pharmacol. Therapeu.* **1996**, *10 (Suppl. 2)*, 107; van Dullemen et al.

Gastroenterology **1995**, *109*, 129) and ulcerative colitis (Masuda et al. *J. Clin. Lab. Immunol.* **1995**, *46*, 111), Jarisch-Herxheimer reactions (Fekade et al. *New England J. Med.* **1996**, *335*, 311), asthma (Amrani et al. *Rev. Malad. Respir.* **1996**, *13*, 539), adult respiratory distress syndrome (Roten et al. *Am. Rev. Respir. Dis.* **1991**, *143*, 590; Suter et al. *Am. Rev. Respir. Dis.* **1992**, *145*, 1016), acute pulmonary fibrotic diseases (Pan et al. *Pathol. Int.* **1996**, *46*, 91), pulmonary sarcoidosis (Ishioka et al. *Sarcoidosis Vasculitis Diffuse Lung Dis.* **1996**, *13*, 139), allergic respiratory diseases (Casale et al. *Am. J. Respir. Cell Mol. Biol.* **1996**, *15*, 35), silicosis (Gossart et al. *J. Immunol.* **1996**, *156*, 1540; Vanhee et al. *Eur. Respir. J.* **1995**, *8*, 834), coal worker's pneumoconiosis (Borm et al. *Am. Rev. Respir. Dis.* **1988**, *138*, 1589), alveolar injury (Horinouchi et al. *Am. J. Respir. Cell Mol. Biol.* **1996**, *14*, 1044), hepatic failure (Gantner et al. *J. Pharmacol. Exp. Therap.* **1997**, *280*, 53), liver disease during acute inflammation (Kim et al. *J. Biol. Chem.* **1997**, *272*, 1402), severe alcoholic hepatitis (Bird et al. *Ann. Intern. Med.* **1990**, *112*, 917), malaria (Grau et al. *Immunol. Rev.* **1989**, *112*, 49; Taverne et al. *Parasitol. Today* **1996**, *12*, 290) including Plasmodium falciparum malaria (Perlmann et al. *Infect. Immunit.* **1997**, *65*, 116) and cerebral malaria (Rudin et al. *Am. J. Pathol.* **1997**, *150*, 257), non-insulin-dependent diabetes mellitus (NIDDM; Stephens et al. *J. Biol. Chem.* **1997**, *272*, 971; Ofei et al. *Diabetes* **1996**, *45*, 881), congestive heart failure (Doyama et al. *Int. J. Cardiol.* **1996**, *54*, 217; McMurray et al. *Br. Heart J.* **1991**, *66*, 356), damage following heart disease (Malkiel et al. *Mol. Med. Today* **1996**, *2*, 336), atherosclerosis (Parums et al. *J. Pathol.* **1996**, *179*, A46), Alzheimer's disease (Fagarasan et al. *Brain Res.* **1996**, *723*, 231; Aisen et al. *Gerontology* **1997**, *43*, 143), acute encephalitis (Ichiyama et al. *J. Neurol.* **1996**, *243*, 457), brain injury (Cannon et al. *Crit. Care Med.* **1992**, *20*, 1414; Hansbrough et al. *Surg. Clin. N. Am.* **1987**, *67*, 69; Marano et al. *Surg. Gynecol. Obstetr.* **1990**, *170*, 32), multiple sclerosis (M.S.; Coyle. *Adv. Neuroimmunol.* **1996**, *6*, 143; Matusevicius et al. *J. Neuroimmunol.* **1996**, *66*, 115) including demyelation and oligiodendrocyte loss in multiple sclerosis (Brosnan et al. *Brain Pathol.* **1996**, *6*, 243), advanced cancer (MucWierzgon et al. *J. Biol. Regulators Homeostatic Agents* **1996**, *10*, 25), lymphoid malignancies (Levy et ~~al.~~ *Crit. Rev. Immunol.* **1996**, *16*, 31), pancreatitis (Exley et al. *Gut* **1992**, *33*, 1126) including systemic complications in acute

pancreatitis (McKay et al. *Br. J. Surg.* **1996**, *83*, 919), impaired wound healing in infection inflammation and cancer (Buck et al. *Am. J. Pathol.* **1996**, *149*, 195), myelodysplastic syndromes (Raza et al. *Int. J. Hematol.* **1996**, *63*, 265), systemic lupus erythematosus (Maury et al. *Arthritis Rheum.* **1989**, *32*, 146), biliary cirrhosis (Miller et al. *Am. J. Gasteroenterolog.* **1992**, *87*, 465), bowel necrosis (Sun et al. *J. Clin. Invest.* **1988**, *81*, 1328), psoriasis (Christophers. *Austr. J. Dermatol.* **1996**, *37*, S4), radiation injury (Redlich et al. *J. Immunol.* **1996**, *157*, 1705), and toxicity following administration of monoclonal antibodies such as OKT3 (Brod et al. *Neurology* **1996**, *46*, 1633). THFα levels have also been related to host-versus-graft reactions (Piguet et al. *Immunol. Ser.* **1992**, *56*, 409) including ischemia reperfusion injury (Colletti et al. *J. Clin. Invest.* **1989**, *85*, 1333) and allograft rejections including those of the kidney (Maury et al. *J. Exp. Med.* **1987**, *166*, 1132), liver (Imagawa et al. *Transplantation* **1990**, *50*, 219), heart (Bolling et al. *Transplantation* **1992**, *53*, 283), and skin (Stevens et al. *Transplant. Proc.* **1990**, *22*, 1924), lung allograft rejection (Grossman et al. *Immunol. Allergy Clin. N. Am.* **1989**, *9*, 153) including chronic lung allograft rejection (obliterative bronchitis; LoCicero et al. *J. Thorac. Cardiovasc. Surg.* **1990**, *99*, 1059), as well as complications due to total hip replacement (Cirino et al. *Life Sci.* **1996**, *59*, 86). THFα has also been linked to infectious diseases (review: Beutler et al. *Crit. Care Med.* **1993**, *21*, 5423; Degre. *Biotherapy* **1996**, *8*, 219) including tuberculosis (Rook et al. *Med. Malad. Infect.* **1996**, *26*, 904), Helicobacter pylori infection during peptic ulcer disease (Beales et al. *Gastroenterology* **1997**, *112*, 136), Chaga's disease resulting from Trypanosoma cruzi infection (Chandrasekar et al. *Biochem. Biophys. Res. Commun.* **1996**, *223*, 365), effects of Shiga-like toxin resulting from E. coli infection (Harel et al. *J. Clin. Invest.* **1992**, *56*, 40), the effects of enterotoxin A resulting from Staphylococcus infection (Fischer et al. *J. Immunol.* **1990**, *144*, 4663), meningococcal infection (Waage et al. *Lancet* **1987**, 355; Ossege et al. *J. Neurolog. Sci.* **1996**, *144*, 1), and infections from Borrelia burgdorferi (Brandt et al. *Infect. Immunol.* **1990**, *58*, 983), Treponema pallidum (Chamberlin et al. *Infect. Immunol.* **1989**, *57*, 2872), cytomegalovirus (CMV; Geist et al. *Am. J. Respir. Cell Mol. Biol.* **1997**, *16*, 31), influenza virus (Beutler~~-et-al~~. *Clin. Res.* **1986**, *34*, 491a), Sendai virus (Goldfield et al. *Proc. Nat'l. Acad. Sci. USA* **1989**, *87*, 1490), Theiler's

encephalomyelitis virus (Sierra et al. *Immunology* **1993**, *78*, 399), and the human immunodeficiency virus (HIV; Poli. *Proc. Nat'l. Acad. Sci. USA* **1990**, *87*, 782; Vyakaram et al. *AIDS* **1990**, *4*, 21; Badley et al. *J. Exp. Med.* **1997**, *185*, 55).

Because inhibition of p38 leads to inhibition of TNFα production, p38 inhibitors will be useful in treatment of the above listed diseases.

A number of diseases are mediated by excess or undesired matrix-destroying metalloprotease (MMP) activity or by an imbalance in the ratio of the MMPs to the tissue inhibitors of metalloproteinases (TIMPs). These include osteoarthritis (Woessner et al. *J. Biol. Chem.* **1984**, *259*, 3633), rheumatoid arthritis (Mullins et al. *Biochim. Biophys. Acta* **1983**, *695*, 117; Woolley et al. *Arthritis Rheum.* **1977**, *20*, 1231; Gravallese et al. *Arthritis Rheum.* **1991**, 34, 1076), septic arthritis (Williams et al. *Arthritis Rheum.* **1990**, *33*, 533), tumor metastasis (Reich et al. *Cancer Res.* **1988**, *48*, 3307; Matrisian et al. *Proc. Nat'l. Acad. Sci., USA* **1986**, *83*, 9413), periodontal diseases (Overall et al. *J. Periodontal Res.* **1987**, *22*, 81), corneal ulceration (Burns et al. *Invest. Opthalmol. Vis. Sci.* **1989**, *30*, 1569), proteinuria (Baricos et al. *Biochem. J.* **1988**, *254*, 609), coronary thrombosis from atherosclerotic plaque rupture (Henney et al. *Proc. Nat'l. Acad. Sci., USA* **1991**, *88*, 8154), aneurysmal aortic disease (Vine et al. *Clin. Sci.* **1991**, *81*, 233), dystrophobic epidermolysis bullosa (Kronberger et al. *J. Invest. Dermatol.* **1982**, *79*, 208), degenerative cartilage loss following traumatic joint injury, osteopenias mediated by MMP activity, tempero mandibular joint disease, and demyelating diseases of the nervous system (Chantry et al. *J. Neurochem.* **1988**, *50*, 688).

Because inhibition of p38 leads to inhibition of MMP production, p38 inhibitors will be useful in treatment of the above listed diseases.

Inhibitors of p38 are active in animal models of TNFα production, including a murine lipopolysaccharide (LPS) model of TNFα production. Inhibitors of p38 are active in a number of standard animal models of inflammatory diseases, including carrageenan-

induced edema in the rat paw, arachadonic acid-induced edema in the rat paw, arachadonic acid-induced peritonitis in the mouse, fetal rat long bone resorption, murine type II collagen-induced arthritis, and Fruend's adjuvant-induced arthritis in the rat. Thus, inhibitors of p38 will be useful in treating diseases mediated by one or more of the above-mentioned cytokines and/or proteolytic enzymes.

The need for new therapies is especially important in the case of arthritic diseases. The primary disabling effect of osteoarthritis, rheumatoid arthritis and septic arthritis is the progressive loss of articular cartilage and thereby normal joint function. No marketed pharmaceutical agent is able to prevent or slow this cartilage loss, although nonsteroidal antiinflammatory drugs (NSAIDs) have been given to control pain and swelling. The end result of these diseases is total loss of joint function which is only treatable by joint replacement surgery. P38 inhibitors will halt or reverse the progression of cartilage loss and obviate or delay surgical intervention.

Several patents have appeared claiming polyarylimidazoles and/or compounds containing polyarylimidazoles as inhibitors of p38 (for example, Lee et al. WO 95/07922; Adams et al. WO 95/02591; Adams et al. WO 95/13067; Adams et al. WO 95/31451). It has been reported that arylimidazoles complex to the ferric form of cytochrome $P450_{cam}$ (Harris et al. *Mol. Eng.* **1995**, *5*, 143, and references therein), causing concern that these compounds may display structure-related toxicity (Howard-Martin et al. *Toxicol. Pathol.* **1987**, *15*, 369). Therefore, there remains a need for improved p38 inhibitors.

Summary of the Invention

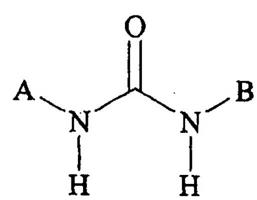
This invention provides compounds, generally described as aryl ureas, including both aryl and heteroaryl analogues, which inhibit p38 mediated events and thus inhibit the production of cytokines (such as TNFα, IL-1 and IL-8) and proteolytic enzymes (such as MMP-1 and MMP-3). The invention also provides a method of treating a cytokine mediated disease state in humans or mammals, wherein the cytokine is one whose

production is affected by p38. Examples of such cytokines include, but are not limited to TNFα, IL-1 and IL-8. The invention also provides a method of treating a protease mediated disease state in humans or mammals, wherein the protease is one whose production is affected by p38. Examples of such proteases include, but are not limited to collagenase (MMP-1) and stromelysin (MMP-3).

Accordingly, these compounds are useful therapeutic agents for such acute and chronic inflammatory and/or immunomodulatory diseases as rheumatoid arthritis, osteoarthritis, septic arthritis, rheumatic fever, bone resorption, postmenopausal osteoperosis, sepsis, gram negative sepsis, septic shock, endotoxic shock, toxic shock syndrome, systemic inflammatory response syndrome, inflammatory bowel diseases including Crohn's disease and ulcerative colitis, Jarisch-Herxheimer reactions, asthma, adult respiratory distress syndrome, acute pulmonary fibrotic diseases, pulmonary sarcoidosis, allergic respiratory diseases, silicosis, coal worker's pneumoconiosis, alveolar injury, hepatic failure, liver disease during acute inflammation, severe alcoholic hepatitis, malaria including Plasmodium falciparum malaria and cerebral malaria, non-insulin-dependent diabetes mellitus (NIDDM), congestive heart failure, damage following heart disease, atherosclerosis, Alzheimer's disease, acute encephalitis, brain injury, multiple sclerosis (MS) including demyelation and oligiodendrocyte loss in multiple sclerosis, advanced cancer, lymphoid malignancies, tumor metastasis, pancreatitis, including systemic complications in acute pancreatitis, impaired wound healing in infection, inflammation and cancer, periodontal diseases, corneal ulceration, proteinuria, myelodysplastic syndromes, systemic lupus erythematosus, biliary cirrhosis, bowel necrosis, psoriasis, radiation injury, toxicity following administration of monoclonal antibodies such as OKT3, host-versus-graft reactions including ischemia reperfusion injury and allograft rejections including kidney, liver, heart, and skin allograft rejections, lung allograft rejection including chronic lung allograft rejection (obliterative bronchitis) as well as complications due to total hip replacement, and infectious diseases including tuberculosis, Helicobacter pylori infection during peptic ulcer disease, Chaga's disease resulting from Trypanosoma cruzi infection, effects of Shiga-like toxin resulting from E.

coli infection, effects of enterotoxin A resulting from Staphylococcus infection, meningococcal infection, and infections from Borrelia burgdorferi, Treponema pallidum, cytomegalovirus, influenza virus, Theiler's encephalomyelitis virus, and the human immunodeficiency virus (HIV).

Accordingly, the present invention is directed to a method for the treatment of diseases mediated by p38, e.g., mediated by one or more cytokines or proteolytic enzymes produced and/or activated by a p38 mediated process, comprising administering a compound of Formula I,

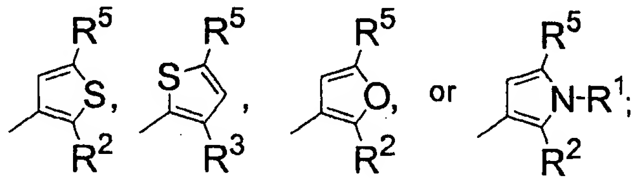


I

wherein

A is C_{6-12}-aryl or C_{5-12}-heteroaryl, each optionally substituted, e.g. by C_{1-4}-alkyl, C_{3-6}-cycloalkyl, halogen, -OH, -OR^1, -NR^1_2;

B is



R^1 is H or C_{1-4}-alkyl;

R^2 and R^3 are each independently halogen, -$COOR^1$, -CN, -$CONR^7R^8$, or -CH_2NHR^9;

R^5 is C_{3-5}-alkyl;

R^6 is C_{1-6}-alkyl;

R^7 is hydrogen;

R^8 is methyl;

R^9 is hydrogen, methyl or -CO-R^{10}; and

R^{10} is hydrogen or methyl optionally substituted by NR^6_2 or $COOR^6$.

In Formula I, suitable heteroaryl groups A include, but are not limited to, 5-10 carbon-atom aromatic rings or ring systems containing 1-2 rings, at least one of which is aromatic, in which one or more, e.g., 1-4 carbon atoms in one or more of the rings can be replaced by oxygen, nitrogen or sulfur atoms. Each ring typically has 5-6 atoms. For example, A can be 2- or 3-thienyl, 1,3,4-thiadiazol-2- or -5-yl, 7-indolyl, or 8-quinolinyl, or additionally optionally substituted phenyl, 2- or 3-thienyl, 1,3,4-thiadiazolyl, etc. For example, A can be 4-methylphenyl, 4-fluorophenyl, 5-methyl-2-thienyl, 4-methyl-2-thienyl or 5-cyclopropyl-1,3,4-thiadiazol-2-yl.

Suitable alkyl groups and alkyl portions of groups, e.g., alkoxy, etc. throughout include methyl, ethyl, propyl, butyl, etc., including all straight-chain and branched isomers such as isopropyl, isobutyl, *sec*-butyl, *tert*-butyl, etc.

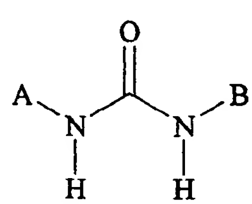
Suitable cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.

Suitable aryl groups include, for example, phenyl and 1- and 2-naphthyl.

Suitable halogen groups include F, Cl, Br, and/or I, from one to per-substitution (i.e. all H atoms on a group replaced by a halogen atom) being possible, mixed substitution of halogen atom types also being possible on a given moiety.

Preferred compounds of Formula I include those where R^2 or R^3 is $-COOR^1$ or $-CONR^7R^8$; R^1 is C[illegible]-alkyl; R^7 is H; and R^8 is methyl, and those where R^5 is isopropyl or *tert*-butyl.

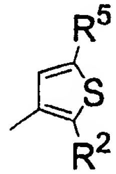
The invention also relates to compounds *per se*, of Formula II



II

wherein

A is C_{6-12}-aryl or C_{5-12}-heteroaryl, each optionally substituted, e.g., by C_{1-4}-alkyl, C_{3-6}-cycloalkyl, halogen, -OH, -OR^1, -NR^1_2;

B is 

R^1 is H or C_{1-4}-alkyl;

R^2 is -$COOR^1$, -$CONR^7R^8$, or -CH_2NHR^9;

R^5 is C_{3-5}-alkyl;

R^6 is C_{1-6}-alkyl;

R^7 is H;

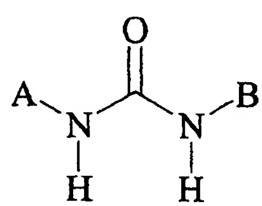
R^8 is methyl;

R^9 is hydrogen, methyl or -CO-R^{10}; and

R^{10} is hydrogen or methyl optionally substituted by NR^6_2 or $COOR^6$,

with the provisos that A is not unsubstituted naphthyl; and if A is unsubstituted phenyl, R^2 is -$COOR^1$ or -$COONR^7R^8$, R^1 is C_{2-4}-alkyl, and R^5 is isopropyl or *tert*-butyl.

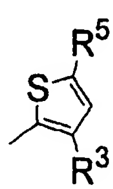
The invention also relates to compounds of Formula III



III

wherein

A is C_{6-12}-aryl or C_{5-12}-heteroaryl, each optionally substituted, e.g., by C_{1-4}-alkyl, C_{3-6}-cycloalkyl, halogen, -OH, -OR^1, -NR^1_2;

B is 

R^1 is H or C_{1-4}-alkyl;

R^3 is -COOR^1, -CONR^{7}R^8, or -CH$_2$NHR^9;

R^5 is C_{3-5}-alkyl;

R^6 is C_{1-6}-alkyl;

R^7 is H;

R^8 is methyl;

R^9 is hydrogen, methyl or -CO-R^{10}; and

R^{10} is hydrogen or methyl optionally substituted by NR$^6{}_2$ or COOR^6,

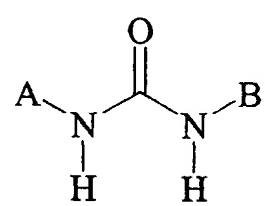
with the provisos that:

(a) A is not unsubstituted naphthyl;

(b) if A is unsubstituted phenyl, then R^3 is -COOR^1 or -CONR^{7}R^8, and R^5 is isopropyl or *tert*-butyl; and

(c) if R^5 is isopropyl, then A is not phenyl substituted by halogen, or -OR^1.

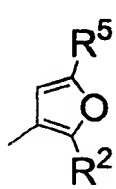
The invention further relates to compounds of Formula IV



IV

wherein

A is C_{6-12}-aryl or C_{5-12}-heteroaryl, each optionally substituted, e.g., by C_{1-4}-alkyl, C_{3-6}-cycloalkyl, halogen, -OH, -OR^1, -NR$^1{}_2$;

B is 

R^1 is H or C_{1-4}-alkyl;

R^2 is -COOR^1, -CONR^{7}R^8, or -CH$_2$NHR^9;

R^5 is C_{3-5}-alkyl;

R^6 is C_{1-6}-alkyl;

R^7 is H;

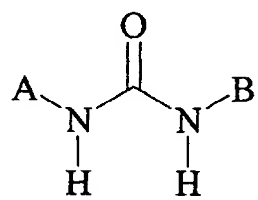
R^8 is methyl;

R^9 is hydrogen, methyl or $-CO-R^{10}$; and

R^{10} is hydrogen or methyl optionally substituted by NR^6_2 or $COOR^6$,

with the proviso that if A is unsubstituted phenyl, R^2 is $COOR^1$ or $-CONR^7R^8$, R^1 is C_{2-4}-alkyl, and R^5 is isopropyl or *tert*-butyl.

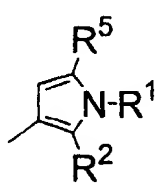
The invention further includes compounds of Formula V



V

wherein

A is C_{6-12}-aryl or C_{5-12}-heteroaryl, each optionally substituted, e.g., by C_{1-4}-alkyl, C_{3-6}-cycloalkyl, halogen, -OH, $-OR^1$, $-NR^1_2$;

B is 

R^1 is H or C_{1-4}-alkyl;

R^2 is $-COOR^1$, $-CONR^7R^8$, or $-CH_2NHR^9$;

R^5 is C_{3-5}-alkyl;

R^6 is C_{1-6}-alkyl;

R^7 is H;

R^8 is methyl;

R^9 is hydrogen, methyl or $-CO-R^{10}$; and

R^{10} is hydrogen or methyl optionally substituted by NR^6_2 or $COOR^6$.

The present invention is also directed to pharmaceutically acceptable salts of Formula I. Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include basic salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, sulphonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid. In addition, pharmaceutically acceptable salts of Formula I may be formed with a pharmaceutically acceptable cation, for instance, in the case when a substituent group comprises a carboxy moiety. Suitable pharmaceutically suitable cations are well known to those skilled in the art, and include alkaline cations (such as Li^+ Na^+ or K^+), alkaline earth cations (such as Mg^{+2}, Ca^{+2} or Ba^{+2}), the ammonium cation, and organic cations, including aliphatic and aromatic substituted ammonium, and quaternary ammonium cations such as those arising from triethylamine, *N,N*-diethylamine, *N,N*-dicyclohexylamine, pyridine, *N,N*-dimethylaminopyridine, 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

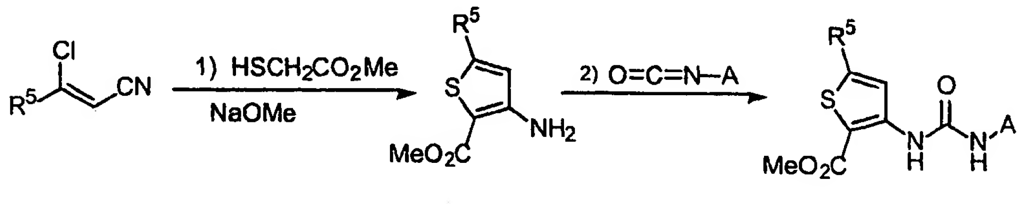
The compounds of Formulae I-V are either known in the art or may be prepared by use of known chemical reactions and procedures. Nevertheless, the following general preparative methods are presented to aid one of skill in the art in synthesizing the inhibitors of the invention, with more detailed particular examples being presented in the experimental section.

General Preparative Methods

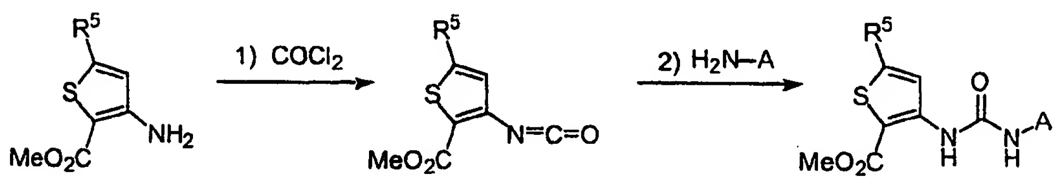
Methyl 5-alkyl-3-aminothiophene-2-carboxylates may be generated by the reaction of methyl thioglycolate with 2-alkyl-2-chloroacrylonitrile in the presence of a base, preferably NaOMe (Ishizaki et al. JP 6025221; Method A). Urea formation may involve

either treatment of the thus formed amine with an isocyanate, or an isocyanate equivalent (Method A), or the conversion of the amine into an isocyanate or an isocyanate equivalent by treatment with phosgene or a phosgene equivalent, followed by reaction with a second amine (Method B).

Method A

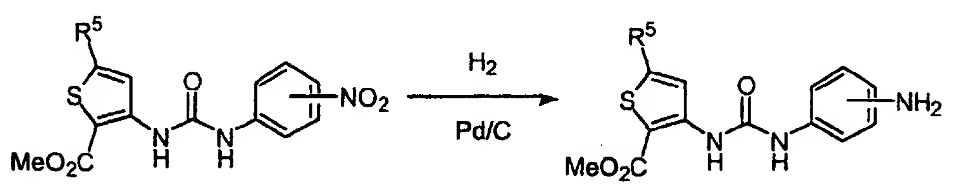


Method B



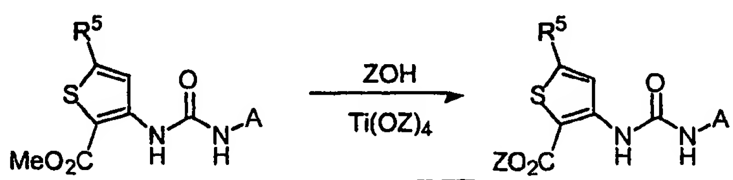
If one or more of the aryl groups is substituted with NO_2, or its equivalent, this moiety may be reduced either using catalytic hydrogenation, eg. with H_2 and palladium-on-carbon, or using a hydride reagent, eg. KBH_4 with CuCl, to give the corresponding amine (Method C).

Method C



Transesterification of the urea may undertaken in alcohol solvent using a Lewis acid catalyst, eg. titanium alkoxide, (Method D).

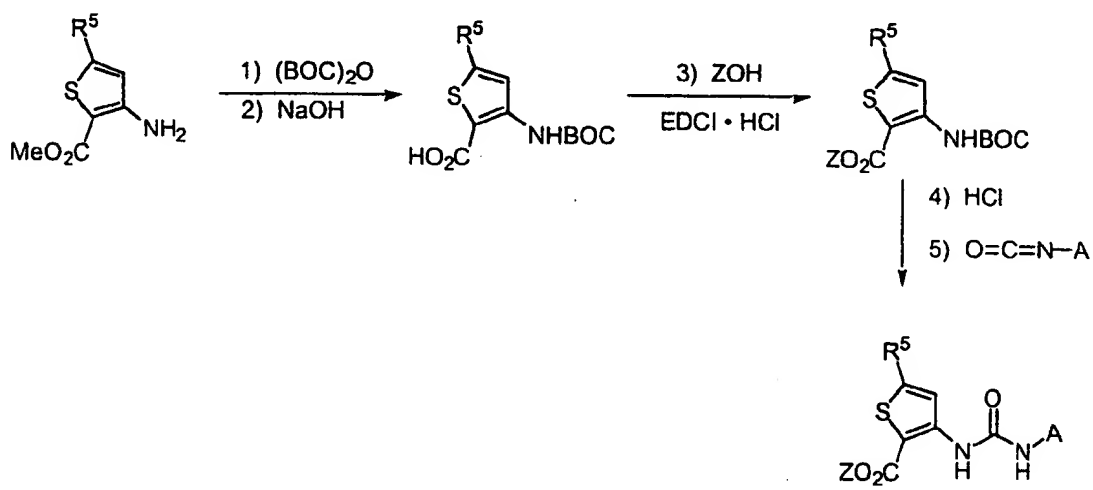
Method D



Alternatively, protection of the amine, eg. as the *tert*-butyl carbamate, followed by saponification of the ester affords the corresponding amino-protected carboxylic acid

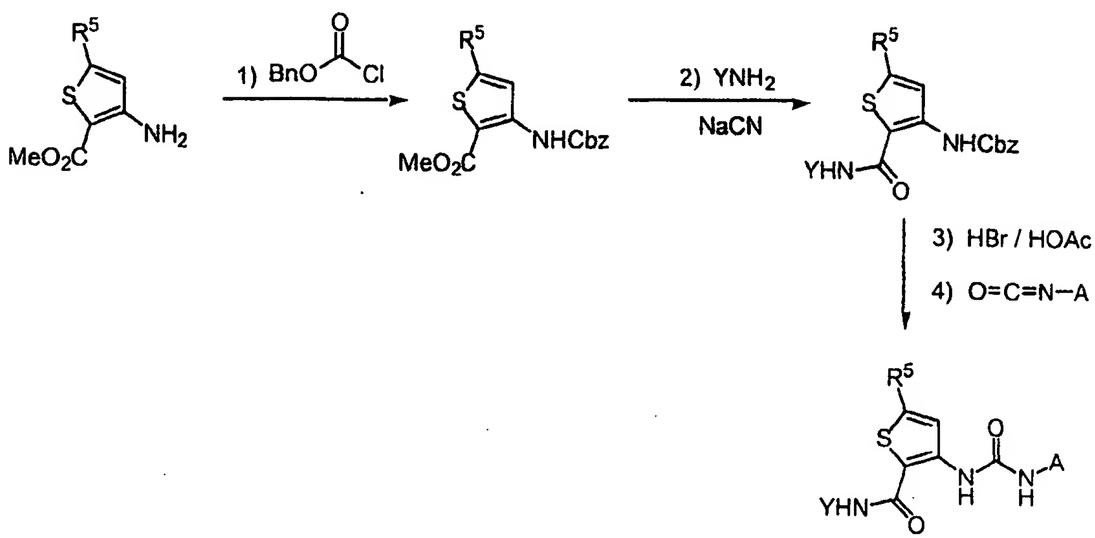
(Method E). Ester formation may employ one of a wide variety of standard protocols, eg. carbodiimide-mediated coupling, depending on the amine protecting group. Finally, deprotection, for example using an acid source such as HCl or trifluoroacetic acid for the *tert*-butyl carbamate, followed by urea formation, as illustrated in either Method A or Method B, will generate ester analogues.

Method E



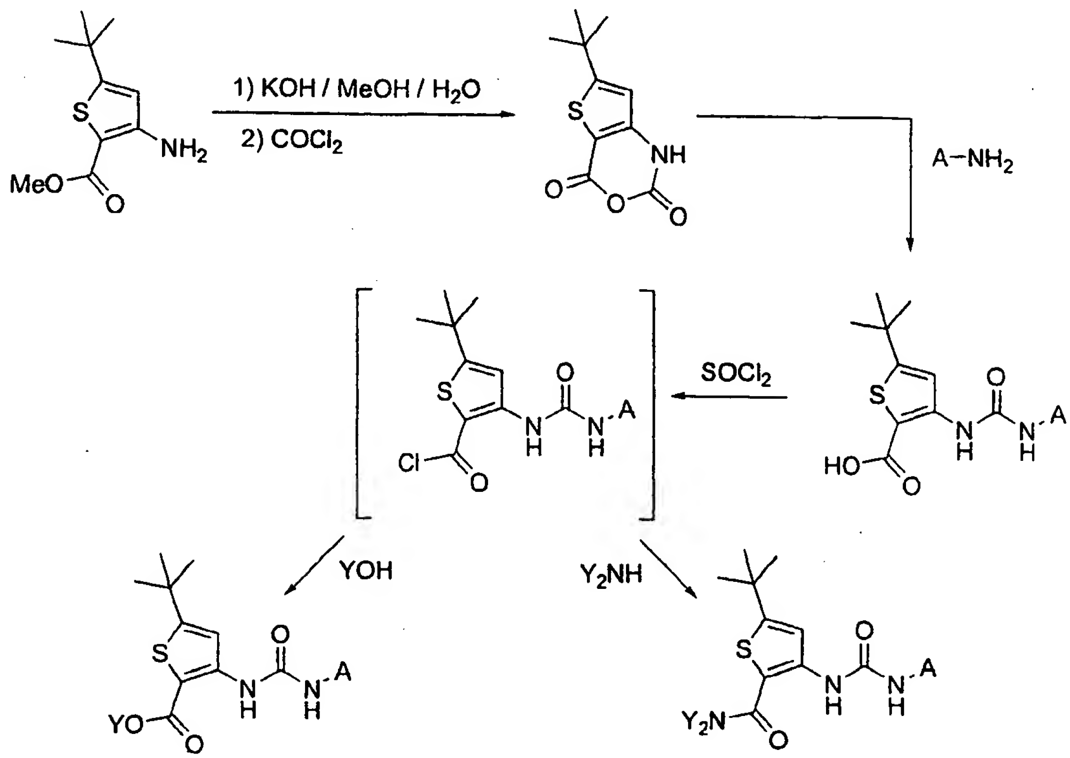
Amide analogues may be generated in a manner similar to that disclosed in Method E. Protection of the amine, eg. as the benzyl carbamate, followed by amide formation, eg. using an amine in the presence of catalytic cyanide, gives the protected amide (Method F). Deprotection, for example with HBr/acetic acid or catalytic hydrogenation for the benzyl carbamate, followed by urea formation as illustrated in Method A will generate amide analogues.

Method F



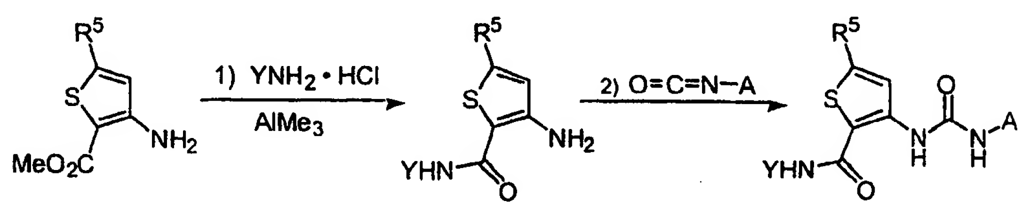
Saponification of 3-aminothiophene-2-carboxylate esters (eg. with KOH) affords the carboxylic acid, which on treatment with phosgene or a phosgene equivalent gives the 2H-thieno[3,2-d]oxazine-2,4(1H)-dione (Method R). Reaction of the thienooxazine with an aryl amine then affords the substituted 2-carboxythienyl urea. Activation, eg. with $SOCl_2$, followed by teratment with an alcohol affords the corresponding ester. Atlternately, treatment of the activated intermediate with a primary or secondary amine affords the corresponding amide.

Method R



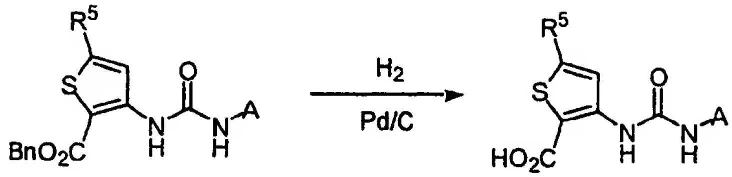
Amide analogues may also be generated by direct treatment of the methyl ester with an aluminum amide (Method G), followed by urea formation as illustrated in Method A.

Method G



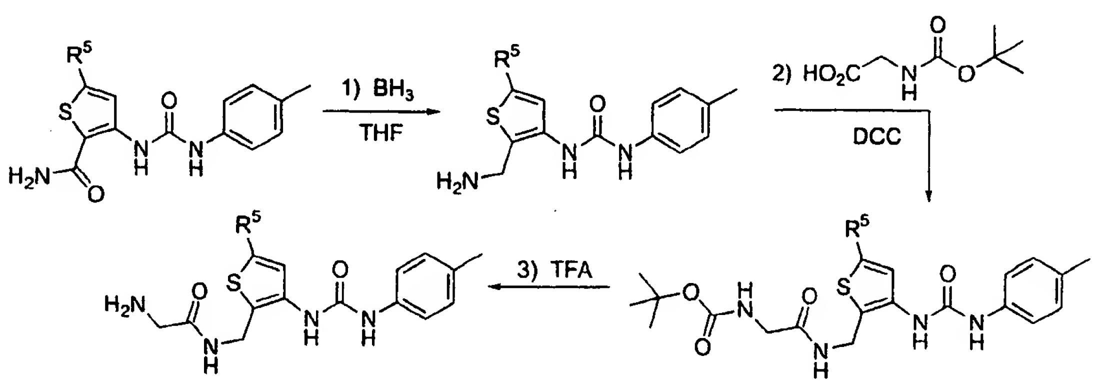
Generation of carboxylic acid analogues may be achieved by hydrolysis of the corresponding esters. For example, catalytic hydrogenation of the C-2 benzyl ester, eg. using H_2 and palladium-on-carbon, provides the thiophene-2-carboxylic acid (Method H).

Method H



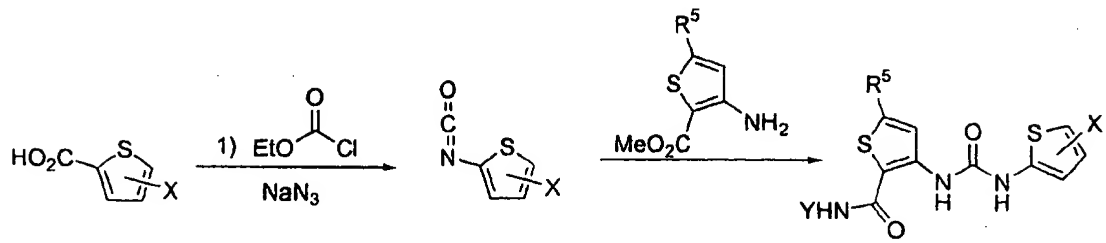
Ureas containing primary amides may be reduced to the aminomethyl analogues using, for example a $BH_3 \cdot THF$ solution (Method I). The thus generated amine may then be functionalized as desired. Amide formation may be achieved using acid chlorides or their equivalent, or through standard coupling protocols. For example, the amine may be coupled with an amino-protected glycine, eg. *N*-BOC-glycine, in the presence of a carbodiimide catalyst, eg. DCC, followed by standard removal of the protecting group, for example using an acid source such as HCl or trifluoroacetic acid for the *tert*-butyl carbamate (Method I).

Method I



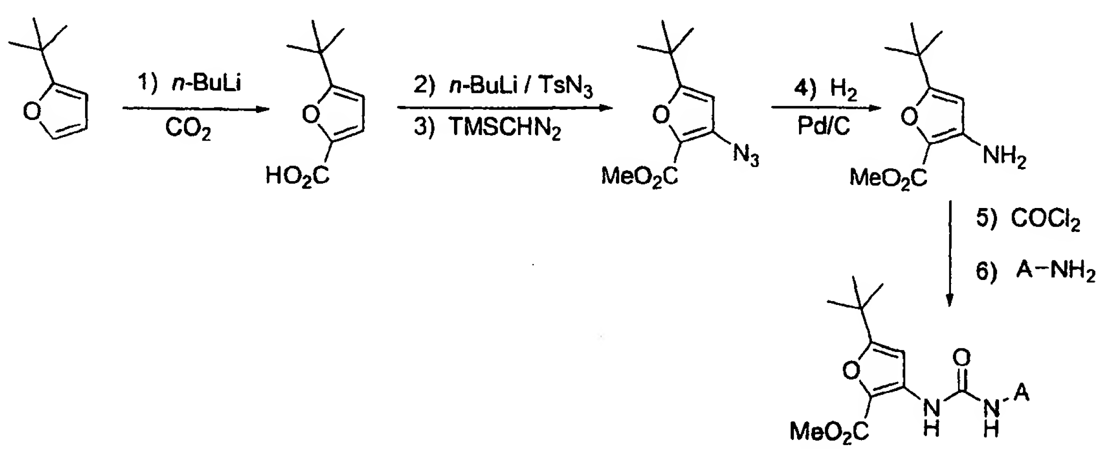
Suitable amines (A-NH_2 with A as in Formulae I-V) may be commercially available, or may be generated through any amine forming reaction, such as use of any variation of the Schmidt rearrangement. Thus, for example, a carboxylic acid may be treated with a phosgene equivalent, such as ethyl chloroformate, and an azide source to generate the isocyanate (Method J). The isocyanate may be treated with water to afford the corresponding amine, or directly reacted with a second amine to afford a urea (Method J).

Method J



Lithiation of 2-alkylfurans, using for example *n*-BuLi, followed by quenching of the 2-furyllithium with CO_2 affords the furan-2-carboxylic acid (Method K). Dianion formation, using for example *n*-BuLi, followed by reaction with tosyl azide, then treatment with a diazomethane equivalent gives the azido ester. Finally, furan analogues of methyl 5-alkyl-3-aminothiophene-2-carboxylates may be generated by reduction of the azide, for example with H_2 and palladium-on-carbon (Method K). The aminofuran analogues may be converted into ureas in a similar manner to that illustrated in either Method A or Method B.

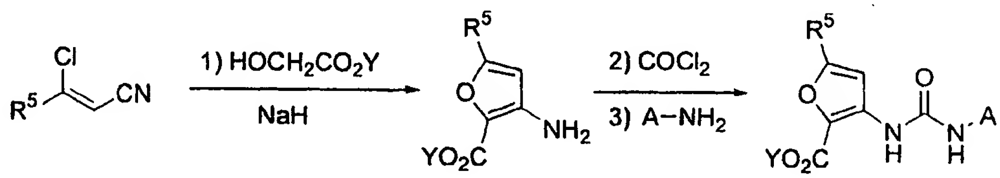
Method K



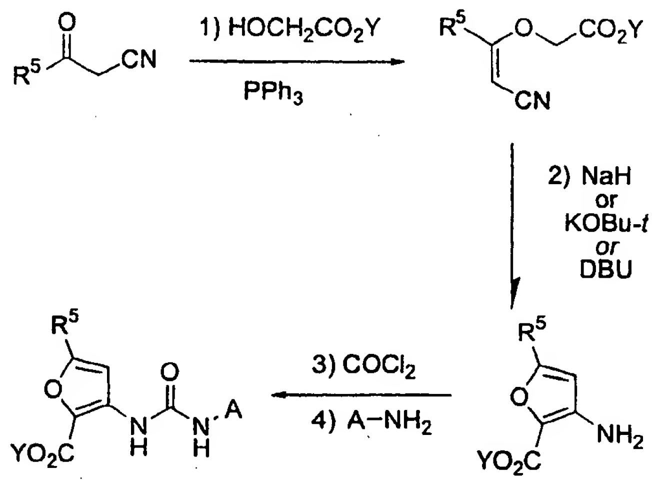
5-Alkyl-3-aminofuran-2-carboxylate esters may also be generated by the reaction of methyl glycolate with 2-alkyl-2-chloroacrylonitrile in the presence of a base (Method L-1). Alternatively, 5-alkyl-3-aminofuran-2-carboxylate esters may be generated from α-cyanoketones (Method L-2). For example, treatment of an α-cyanoketones with an alkyl glycolate under Mitsunobu conditions (eg. ~~-~~triphenylphosphine and a dialkyl azodicarboxylate) affords the β-cyano enol ether. Treatment of the enol ether with a

suitable base, such as KOBu-*t*, NaH, or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), then generates the desired aminofuran. Aminofuran analogues may be converted into ureas in a similar manner to that illustrated in either Method A or Method B.

Method L-1

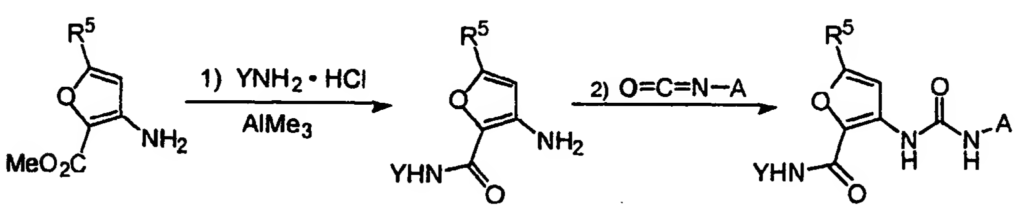


Method L-2



Amide analogues of aminofurancarboxylic acids may be generated by direct treatment of the methyl ester (fromL-1 or L-2) with an aluminum amide (Method M), followed by urea formation as illustrated in Method A.

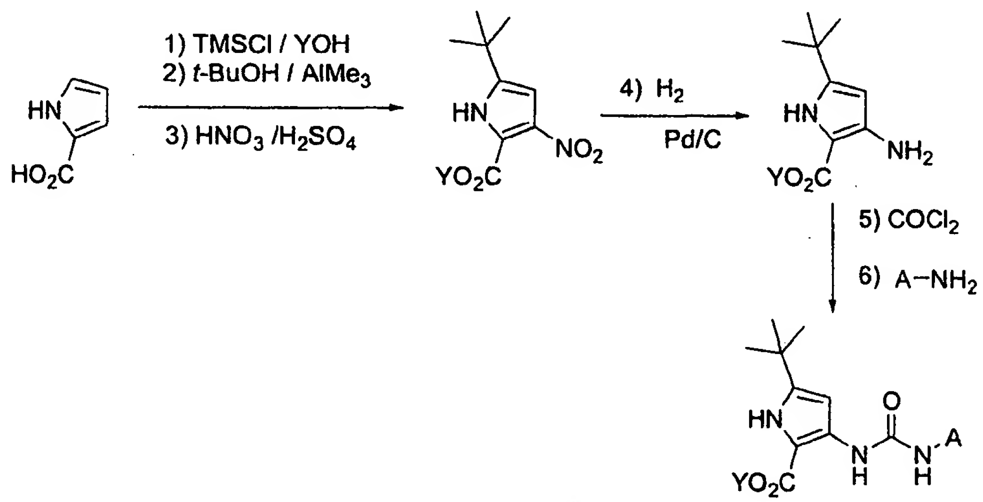
Method M



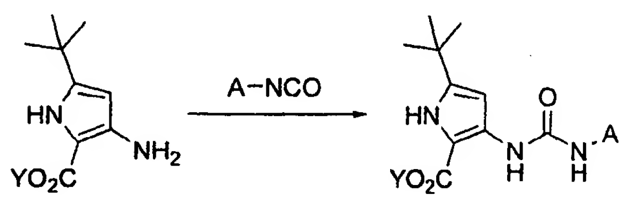
Esterification of pyrrole-2-carboxylic acid followed by Friedel-Crafts alkylation affords the 5-alkyl analogue (Method N-1). Electrophilic nitration of the pyrrole with nitric acid in sulfuric acid affords a separable mixture of the 3-nitro compound shown below and the

3,4-dinitro analogue (Method N-1). Reduction of the nitro group, for example using hydrogen and palladium-on-carbon, affords the amine, which may be converted into the urea in a manner similar to that illustrated in Method B (Method N-1), or on treatment with an isocyanate (Method N-2).

Method N-1

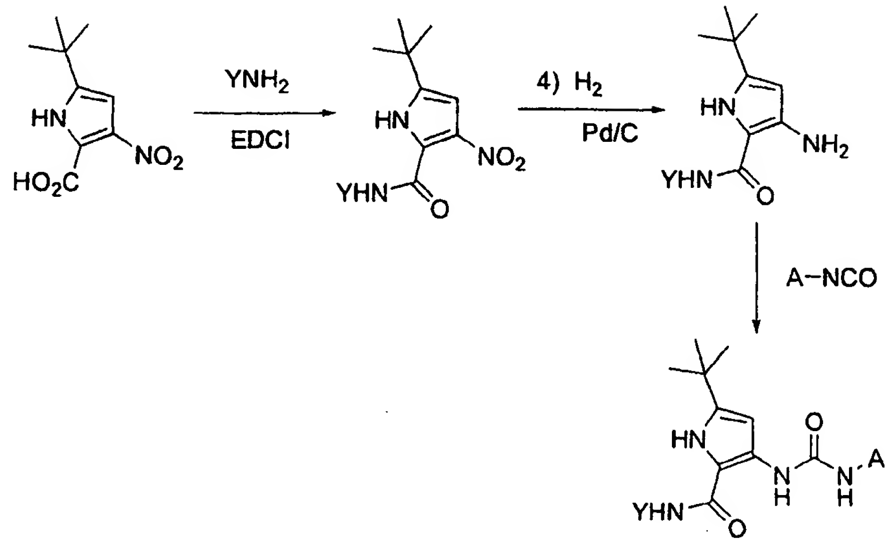


Method N-2



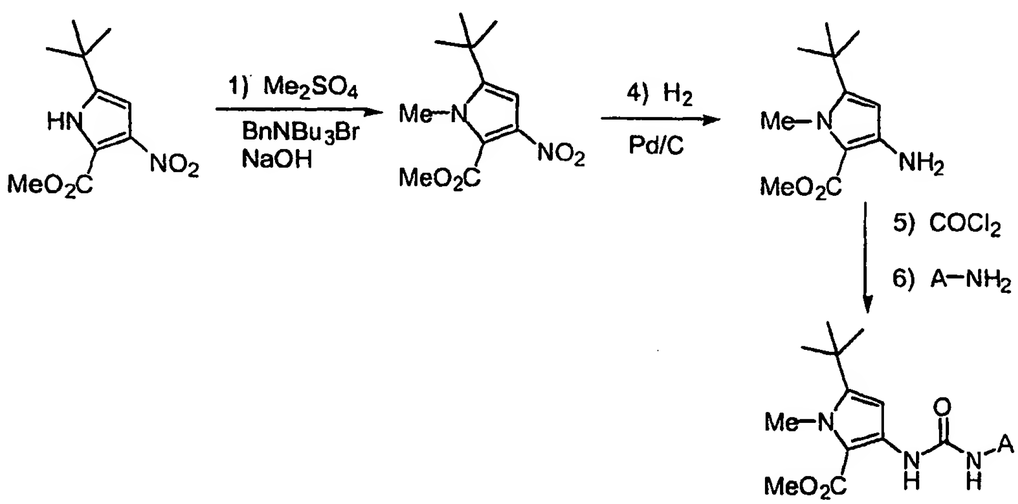
As shown in Method N-3, amide analogues of pyrroles may be generated by conversion of the 5-alkyl-3-nitropyrrole-2-carboxylic acid into the corresponding amide using standard coupling conditions (eg. 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, EDCI), followed by reduction of the nitro group and urea formation, as illustrated in Methods N-1 and N-2.

Method N-3



The 3-nitropyrrole generated in Method N-1 may also be treated with alkylating agents to form the *N*-alkyl-3-nitropyrrole (Method O). Reduction of the nitro moiety and urea formation proceed in a manner similar to that illustrated in Method N-1.

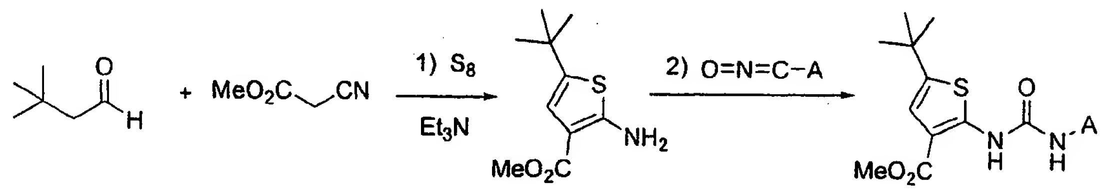
Method O



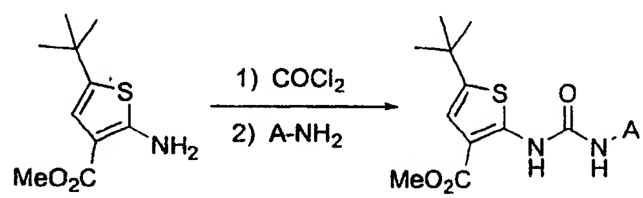
Methyl 5-*tert*-butyl-2-aminothiophene-3-carboxylates may be generated by the reaction of methyl cyanoacetate with 3,3-dimethylbutyraldehyde in the presence of elemental sulfur (Gewald et al. *Chem. Ber.* **1966**, *99*, 94; Method P). Urea formation may either involve treatment of the thus formed amine with an isocyanate, or an isocyanate equivalent (Method P), or the convertion of the amine into an isocyanate or an isocyanate

equivalent by treatment with phosgene(Method Q) or a phosgene equivalent (Methods S and T), followed by reaction with a second amine.

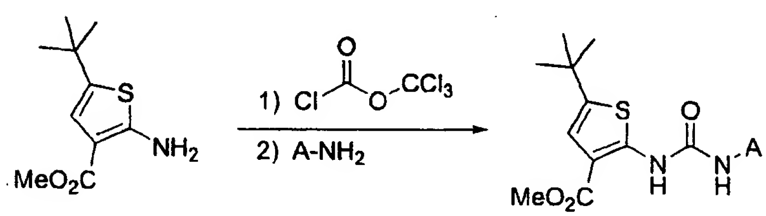
Method P



Method Q

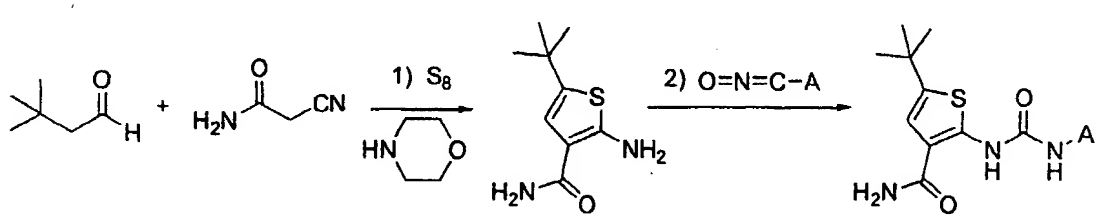


Methods S and T



Similarly, formation of the 3-carbamoyl-2-thienylamine followed by treatment with an isocyanate affords the corresponding urea (Method U).

Method U



The invention also includes pharmaceutical compositions including a compound of Formulae I-V, and a physiologically acceptable carrier.

The compounds may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations. The term 'administration by injection' includes intravenous, intramuscular, subcutaneous and parenteral injections, as well as use of infusion techniques. One or more compounds may be present in association with one or more non-toxic pharmaceutically acceptable carriers and if desired other active ingredients.

Compositions intended for oral use may be prepared according to any suitable method known to the art for the manufacture of pharmaceutical compositions. Such compositions may contain one or more agents selected from the group consisting of diluents, sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; and binding agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. These compounds may also be prepared in solid, rapidly released form.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions containing the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions may also be used. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropyl-methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or *n*-propyl, *p*-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, sweetening, flavoring and coloring agents, may also be present.

The compounds may also be in the form of non-aqueous liquid formulations, e.g., oily suspensions which may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or peanut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oil phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

The compounds may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols.

For all regimens of use disclosed herein for compounds of Formulae I-V, the daily oral dosage regimen will preferably be from 0.01 to 200 mg/Kg of total body weight. The daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous and parenteral injections, and use of infusion techniques will preferably be from 0.01 to 200 mg/Kg of total body weight. The daily rectal dosage regimen will preferably be from 0.01 to 200 mg/Kg of total body weight. The daily topical dosage regimen will preferably be from 0.1 to 200 mg administered between one to four times daily. The daily inhalation dosage regimen will preferably be from 0.01 to 10 mg/Kg of total body weight.

It will be appreciated by those skilled in the art that the particular method of administration will depend on a variety of factors, all of which are considered routinely when administering therapeutics. It will also be appreciated by one skilled in the art that the specific dose level for a given patient depends on a variety of factors, including specific activity of the compound administered, age, body weight, health, sex, diet, time and route of administration, rate of excretion, etc. It will be further appreciated by one skilled in the art that the optimal course of treatment, ie, the mode of treatment and the daily number of doses of a compound of Formulae I-V or a pharmaceutically acceptable salt thereof given for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment tests.

The entire enclosure of all applications, patents and publications cited above and below are hereby incorporated by reference.

The following examples are for illustrative purposes only and are not intended, nor should they be construed to limit the invention in any way.

EXAMPLES

All reactions were performed in flame-dried or oven-dried glassware under a positive pressure of dry argon or dry nitrogen, and were stirred magnetically unless otherwise indicated. Sensitive liquids and solutions were transferred via syringe or cannula, and introduced into reaction vessels through rubber septa. Unless otherwise stated, the term 'concentration under reduced pressure' refers to use of a Buchi rotary evaporator at approximately 15 mmHg. Bulb-to-bulb concentrations were conducted using an Aldrich Kugelrohr apparatus, and in these cases temperatures refer to oven temperatures.

All temperatures are reported uncorrected in degrees Celcius (°C). Unless otherwise indicated, all parts and percentages are by volume.—

Commercial grade reagents and solvents were used without further purification, except that tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME) were doubly distilled from potassium, diethyl ether was distilled from sodium benzophenone ketyl, and CH_2Cl_2 was distilled from CaH_2.

Thin-layer chromatography (TLC) was performed on Whatman® pre-coated glass-backed silica gel 60A F-254 250 µm plates. Visualization of plates was effected by one or more of the following techniques: (a) ultraviolet illumination, (b) exposure to iodine vapor, (c) immersion of the plate in a 10% solution of phosphomolybdic acid in ethanol followed by heating, (d) immersion of the plate in a cerium sulfate solution followed by heating, and/or (e) immersion of the plate in an acidic ethanol solution of 2,4-dinitrophenylhydrazine followed by heating. Column chromatography (flash chromatography) was performed using 230-400 mesh EM Science® silica gel. Rotary chromatography was performed using pre-cast SiO_2 plates (Alltech®) on a Harrison Research Chromatotron.

Melting points (mp) were determined using a Thomas-Hoover melting point apparatus or a Mettler FP66 automated melting point apparatus and are uncorrected. Fourier transform infrared sprectra were obtained using a Mattson 4020 Galaxy Series spectrophotometer. Proton (^1H) nuclear magnetic resonance (NMR) spectra were measured with a General Electric GN-Omega 300 (300 MHz) spectrometer with either Me_4Si (d 0.00) or residual protonated solvent ($CHCl_3$ δ 7.26; MeOH δ 3.30; DMSO δ 2.49) as standard. Carbon (^{13}C) NMR spectra were measured with a General Electric GN-Omega 300 (75 MHz) spectrometer with solvent ($CDCl_3$ δ 77.0; MeOD-d_3; δ 49.0; DMSO-d_6 δ 39.5) as standard. Low resolution mass spectra (MS) and high resolution mass spectra (HRMS) were either obtained as electron impact (EI) mass spectra or as fast atom bombardment (FAB) mass spectra. Electron impact mass spectra (EI-MS) were obtained with a Hewlett Packard 5989A mass spectrometer equipped with a Vacumetrics Desorption Chemical Ionization Probe for sample introduction. The ion source was maintained at 250 °C. Electron impact ionization was performed with electron energy of

70 eV and a trap current of 300 μA. Liquid-cesium secondary ion mass spectra (FÁB-MS), an updated version of fast atom bombardment were obtained using a Kratos Concept 1-H spectrometer. Chemical ionization mass spectra (CI-MS) were obtained using a Hewlett Packard MS-Engine (5989A) with methane or ammonia as the reagent gas ($1x10^{-4}$ torr to $2.5x10^{-4}$ torr). The direct insertion desorption chemical ionization (DCI) probe (Vaccumetrics, Inc.) was ramped from 0-1.5 amps in 10 sec and held at 10 amps until all traces of the sample disappeared (~1-2 min). Spectra were scanned from 50-800 amu at 2 sec per scan. HPLC - electrospray mass spectra (HPLC ES-MS) were obtained using a Hewlett-Packard 1100 HPLC equipped with a quaternary pump, a variable wavelength detector, a C-18 column, and a Finnigan LCQ ion trap mass spectrometer with electrospray ionization. Spectra were scanned from 120-800 amu using a variable ion time according to the number of ions in the source. Gas chromatography - ion selective mass spectra (GC-MS) were obtained with a Hewlett Packard 5890 gas chromatograph equipped with an HP-1 methyl silicone column (0.33 mM coating; 25 m x 0.2 mm) and a Hewlett Packard 5971 Mass Selective Detector (ionization energy 70 eV). Elemental analyses are conducted by Robertson Microlit Labs, Madison NJ.

All compounds displayed NMR spectra, LRMS and either elemental analysis or HRMS consistant with assigned structures.

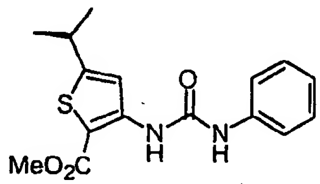
List of Abbreviations and Acryonyms

AcOH	acetic acid
CI	chemical ionization
DMAP	4-(*N,N*-dimethylamino)pyridine
DMF	*N,N*-dimethylformamide
DME	1,2-dimethoxyethane
DMSO	dimethyl sulfoxide
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
EI	electron impact
Et_3N	triethylamine
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
FAB	fast atom bombardment
GC-MS	gas chromatography mass spectrum
hex	*n*-hexane
FTIR	Fourier transform infrared
HPLC ES-MS	high pressure liquid chromatography electrospray mass spectrum
HRMS	high resolution mass spectrum
KOAc	potassium acetate
LRMS	low resoultion mass spectrum
MeOH	methanol
NaOMe	sodium methoxide
pet. ether	petroleum ether (boiling range 30-60 °C)
THF	tetrahydrofuran
$Ti(OEt)_4$	tetraethoxytitanium(IV)
TMSCl	trimethylsilyl chloride
TLC	thin layer chromatography
$TMSCHN_2$	(trimethylsilyl)diazomethane

General Methods for the Synthesis of Urido Heterocycles

Method A

Synthesis of *N*-(2-carbomethoxy-5-isopropyl-3-thienyl)-*N'*-(phenyl)urea (Example 1).



Step 1

To a solution of NaOMe (14 g) in MeOH (1 L) was added methyl thioglycolate (22.3 mL). The mixture was stirred for 5 min, then a solution of 3-chloro-4-methyl-2-pentenenitrile (32.4 g) in MeOH (200 mL) was added and the solution was heated at the reflux temp. for 90 min. After cooling to 20 °C, the mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc, washed with a 1N HCl solution, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexane) to yield methyl 3-amino-5-isopropylthiophene-2-carboxylate (8.0 g, 16%).

Step 2

To a solution of methyl 3-amino-5-isopropylthiophene-2-carboxylate (0.050 g, 0.25 mmol) in toluene (1 mL) was added phenyl isocyanate (0.024 mL, 0.25 mmol, 1.0 equiv) and the resulting mixture was heated at the reflux temp. for 6 h, then cooled to 20 °C during which *N*-(2-carbomethoxy-5-isopropyl-3-thienyl)-*N'*-(phenyl)urea crystallized from solution (0.014 g, 18%): mp 108-10 °C; ^1H NMR ($CDCl_3$) δ 1.3 (d, 6H), 3.1 (m, 1H), 3.8 (s, 3H), 6.7 (br s, 1H), 7.2 (m, 1H), 7.3 (m, 3H), 7.83 (s, 1H); EI-LRMS *m/z* 318 (M^+).

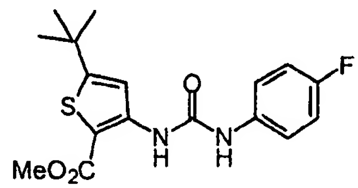
Selected compound synthesized using Method A:

N-(2-Carbomethoxy-5-*tert*-butyl-3-thienyl)-*N'*-(4-methylphenyl)urea (Example 5): mp 124-6 °C; ^1H NMR ($CDCl_3$) δ 1.34 (s, 9H), 2.30 (s, 3H), 3.76 (s, 3H), 7.12 (d, *J*=8.5 Hz, 2H), 7.29 (d, *J*=8.5 Hz, 2H), 7.48 (br s, 1H), 7.87 (s, 1H), 9.67 (s, 1H); ^{13}C NMR ($CDCl_3$)

δ 20.8, 31.7 (3C), 35.2, 51.6, 104.9, 117.2, 121.4 (2C), 129.7 (2C), 134.0, 135.1, 145.9, 152.2, 164.4, 165.0.

Method B

Synthesis of *N*-(2-carbomethoxy-5-*tert*-butyl-3-thienyl)-*N'*-(4-fluorophenyl)urea (Example 54).



Step 1

To a solution of phosgene (1.93M in toluene, 7.9 mL, 15.2 mmol, 3.0 equiv) in CH_2Cl_2 (100 mL) at 0 °C was added a solution of methyl 3-amino-5-*tert*-butylthiophene-2-carboxylate (1.08 g, 5.07 mmol) and pyridine (1.6 mL, 20.3 mmol, 4.0 equiv) in CH_2Cl_2 (30 mL). The reaction mixture was allowed to slowly warm to room temp. and was stirred at that temp. for 30 min. The resulting slurry was concentrated under reduced pressure to give a mixture of 2-carbomethoxy-5-*tert*-butyl-3-thienyl isocyanate and pyridinium hydrochloride as a yellow solid. 2-Carbomethoxy-5-*tert*-butyl-3-thienyl isocyanate: ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 9H), 3.89 (s, 3H), 6.55 (s, 1H). The mixture was used in the next step without further puirification.

Step 2

The 2-carbomethoxy-5-*tert*-butyl-3-thienyl isocyanate prepared in Method B, Step 1 was dissolved in anh. THF (100 mL). 4-Fluoroaniline (1.13 g, 10.1 mmol, 2.0 equiv) was added and the resulting solution was stirred at room temp. for 14 h. The resulting mixture was diluted with $CHCl_3$ (200 mL) then washed with a 1N HCl solution (2 x 100 mL) and a saturated NaCl solution (100 mL). The combined aqueous layers were back-extracted with $CHCl_3$ (100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give a yellow-brown solid (1.61 g), which was recrystallized (CH_2Cl_2) to give *N*-(2-carbomethoxy-5-*tert*-butyl-3-thienyl)-*N'*-(4-

fluorophenyl)urea as a white solid (1.34 g, 75% over 2 steps): mp 160-2 °C; TLC (20% EtOAc/hexane) R_f 0.45; ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 9H), 3.77 (s, 3H), 7.01 (dd, *J*=8.8, 8.5 Hz, 2H), 7.34-7.39 (m, 2H), 7.49 (s, 1H), 7.82 (s, 1H), 9.68 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 31.7 (3C), 35.2, 51.6, 105.1, 115.9 (d, J_{C-F}=22.0 Hz, 2C), 117.1, 123.2 (d, J_{C-F}=7.3 Hz, 2C), 133.7 (d, J_{C-F}=2.4 Hz, 1C), 145.8, 148.6, 152.2, 159.6 (d, J_{C-F}=244.1 Hz, 1C), 164.7, 165.1; FAB-LRMS *m/z* (rel abundance) 351 (M + H, 33%).

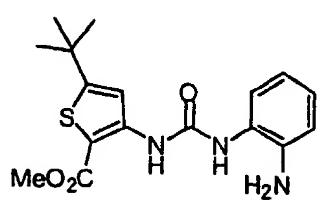
Selected compounds synthesized using Method B:

N-(2-Carbomethoxy-5-*tert*-butyl-3-thienyl)-*N'*-(3-methylphenyl)urea (Example 9): mp 70-2 °C; ^{1}H NMR ($CDCl_3$) δ 1.4 (s, 9H), 2.4 (s, 3H), 3.8 (s, 3H), 6.75 (br s, 1H), 6.95 (d, 1H), 7.2-7.3 (m, 3H), 7.8 (s, 1H), 9.7 (s, 1H); FAB-LRMS *m/z* (rel abundance) 347 (M + H, 56%).

N-(2-Carbomethoxy-5-*tert*-butyl-3-thienyl)-*N'*-(5-cyclopropyl-2-thiadiazolyl)urea (Example 16): ^{1}H NMR ($CDCl_3$) δ 1.20-1.40 (m, 4H), 1.40 (s, 9H), 2.25-2.35 (m, 1H), 3.80 (s, 3H), 7.75 (s, 1H), 10.00 s, 1H); FAB-LRMS *m/z* (rel abundance) 381 (M + H, 18%).

Method C

Synthesis of *N*-(2-carbomethoxy-5-*tert*-butyl-3-thienyl)-*N'*-(2-aminophenyl)urea (Example 11).



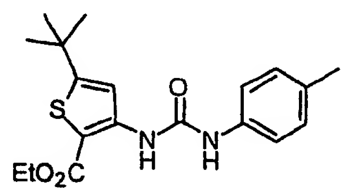
N-(2-Carbomethoxy-5-*tert*-butyl-3-thienyl)-*N'*-(2-nitrophenyl)urea was synthesized in a manner analogous to that described in Method B.

A slurry of *N*-(2-carbomethoxy-5-*tert*-butyl-3-thienyl)-*N'*-(2-nitrophenyl)urea (0.078 g, 0.21 mmol) and 10% Pd/C (0.010 g) in MeOH (15 mL) was stirred under H_2 (1 atm.) for

18 h at 20 °C. Celite® was added and the slurry was filtered. The resulting solution was concentrated under reduced pressure and the residue was purified by flash chromatography (gradient from 20% EtOAc/hexane to 50% EtOAc/hexane) to afford *N*-(2-carbomethoxy-5-*tert*-butyl-3-thienyl)-*N'*-(2-aminophenyl)urea as a foam (0.060 g, 83%): ^{1}H NMR ($CDCl_3$, partial spectrum) δ 1.4 (s, 9H), 3.6 (s, 3H), 6.8-7.3 (m, 4H), 7.8 (s, 1H), 9.6 (s, 1H); FAB-LRMS *m/z* (rel abundance) 348 (M + H, 34%).

Method D

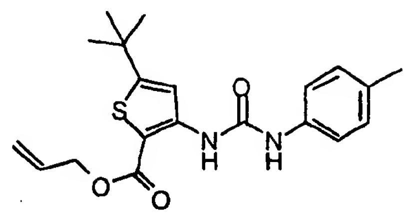
Synthesis of *N*-(2-carboethoxy-5-*tert*-butyl-3-thienyl)-*N'*-(4-methylphenyl)urea (Example 6).



A solution of $Ti(OEt)_4$ (0.10 mL, 0.476 mmol, 11.8 equiv), *N*-(2-carbomethoxy-5-*tert*-butyl-3-thienyl)-*N'*-(4-methylphenyl)urea (0.014 g, 0.040 mmol), and EtOH (10 mL) was heated at the reflux temp. for 36 h. The resulting mixture was filtered and the filtrate was concentrated under reduced pressure. The residual oil was dissolved in EtOAc and purified by flash chromatography (gradient from 10% EtOAc/hexane to 20% EtOAc/hexane) to afford *N*-(2-carboethoxy-5-*tert*-butyl-3-thienyl)-*N'*-(4-methylphenyl)urea (0.0086 g, 59%): ^{1}H NMR ($CDCl_3$) δ 1.30 (d, *J*=7.4 Hz, 3H), 1.35 (s, 9H), 2.30 (s, 3H), 4.24 (q, *J*=7.4 Hz, 2H), 7.11 (d, *J*= 8.5Hz, 2H), 7.29 (d, *J*= 8.5 Hz, 2H), 7.30 (br s, 1H), 7.86 (s, 1H), 9.68 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.3, 20.8, 31.8 (3C), 35.2, 60.6, 105.1, 117.2, 121.0 (2C), 129.7 (2C), 133.8, 135.2, 145.9, 152.1, 164.2, 164.8.

Method E

Synthesis of *N*-(2-(carbo-1-prop-2-enyloxy)-5-*tert*-butyl-3-thienyl)-*N'*-(4-methylphenyl)urea (Example 8).



Step 1

To a solution of methyl 3-amino-5-*tert*-butylthiophene-2-carboxylate (10.0 g, 47 mmol) and DMAP (6.57 g, 47 mmol, 1.0 equiv) in pyridine (188 mL) at 0 °C was added di-*tert*-butyl dicarbonate (11.3 g, 51.7 mmol, 1.1 equiv). The pyridine solution was allowed to warm to room temp. and was stirred for 6 d. The resulting mixture was concentrated under reduced pressure to yield an orange solid, which was separated between CH_2Cl_2 (250 mL) and a 1M H_3PO_4 solution (100 mL). The organic phase was washed with a saturated $NaHCO_3$ solution (100 mL) and a saturated NaCl solution (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The resulting light orange solid was recrystallized (EtOH/H_2O) to give methyl 3-(*N*-carbo-*tert*-butoxyamino)-5-*tert*-butylthiophene-2-carboxylate as an off-white solid (12.00 g, 82%): TLC (10% EtOAc) R_f 0.65; ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 9H), 1.51 (s, 9H), 3.84 (s, 3H), 7.68 (s, 1H) 9.35 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.6 (3C), 32.0 (3C), 35.4, 51.8, 81.1, 105.2, 116.6, 145.7, 152.4, 164.5, 165.0.

Step 2

To a solution of methyl 3-(*N*-carbo-*tert*-butoxyamino)-5-*tert*-butylthiophene-2-carboxylate (10.7 g, 34.1 mmol) in a 2:1:1 mixture of THF, MeOH and H_2O (340 mL) was added NaOH (4.09 g, 102.3 mmol, 3.0 equiv). The resulting solution was heated at 60 °C for 18 h, cooled to room temp. and concentrated under reduced pressure. The residue was separated between H_2O (500 mL) and EtOAc (250 mL). The aqueous phase was adjusted to pH 2 with a 10% HCl solution, then extracted with EtOAc (2 x 400 mL). The organic phase was washed with a saturated NaCl solution (250 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford 3-(*N*-carbo-*tert*-butoxyamino)-5-*tert*-butylthiophene-2-carboxylic acid as an orange solid (6.6 g, 65%). This material was used in the next step without further purification. An analytical sample of the carboxylic acid

was further purified: mp 187-8 °C, TLC (10% MeOH/CH_2Cl_2) R_f 0.17; ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9H), 1.54 (s, 9H), 7.73 (s, 1H), 9.19 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.2 (3C), 31.8 (3C), 35.4, 81.3, 104.6, 116.7, 146.7, 151.9, 166.6, 169.3; FAB-LRMS *m/z* (rel abundance) 300 (M + H, 30%).

Step 3

To a solution of 3-(*N*-carbo-*tert*-butoxyamino)-5-*tert*-butylthiophene-2-carboxylic acid (0.20 g, 0.67 mmol), allyl alcohol (0.042 g, 0.73 mmol, 1.1 equiv) and DMAP (0.008 g, 0.07 mmol, 10 mol%) in CH_2Cl_2 (2 mL) was added EDCI·HCl (0.14 g, 0.73 mmol, 1.1 equiv). The CH_2Cl_2 mixture was stirred at room temp. for 3 d, diluted with CH_2Cl_2, washed with a 1N HCl solution (5 mL) and a saturated $NaHCO_3$ solution (5 mL), dried (Na_2SO_4), and concentrated under reduced pressure to afford allyl 3-(*N*-carbo-*tert*-butoxyamino)-5-*tert*-butylthiophene-2-carboxylate (0.15 g, 65%) as a colorless oil: TLC (50% CH_2Cl_2/hexane) R_f 0.63; ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 9H), 1.50 (s, 9H), 4.74 (ddd, *J*=5.5, 1.5, 1.5 Hz, 2H), 5.26 (dd, *J*=10.3, 1.5 Hz, 1H), 5.37 (dd, *J*=17.3, 1.5 Hz, 1H), 5.87-5.98 (m, 1H), 7.68, 9.35; ^{13}C NMR ($CDCl_3$) δ 28.2 (3C), 31.8 (3C), 35.2, 64.9, 80.8, 104.9, 116.4, 118.1, 132.0, 145.6, 152.1, 164.0, 164.4

Step 4

Allyl 3-(*N*-carbo-*tert*-butoxyamino)-5-*tert*-butylthiophene-2-carboxylate (0.14 g, 0.41 mmol) was dissolved in solution of HCl in dioxane (4N, 11.0 mL, 4.1 mmol, 10 equiv). The resulting solution was stirred at room temp. for 5 d, diluted with $CHCl_3$ (5 mL), washed with a 1N HCl solution (5 mL) and a saturated NaCl solution (5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was filtered through a plug of SiO_2 with the aid of a 10% EtOAc/CH_2Cl_2 solution to give allyl 3-amino-5-*tert*-butylthiophene-2-carboxylate as a yellow oil (0.088 g, 95%): ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 9H), 4.72 (ddd, *J*=4.1, 1.5, 1.5 Hz, 2H), 5.21 (ddd, *J*=10.3, 2.9, 1.5 Hz, 1H), 5.36 (ddd, J=17.3, 3.1, 1.5, 1H), 5.42 (br s, 2H), 5.92-6.03 (m, 1H), 6.34 (s, 1H). This material was used without further purification.

Step 5

To a solution of allyl 3-amino-5-*tert*-butylthiophene-2-carboxylate (0.088 g, 0.39 mmol) and pyridine (0.12 g, 1.56 mmol, 4.0 equiv) in CH_2Cl_2 (4 mL) at 0 °C was added a solution of phosgene in toluene (1.93M, 0.6 mL, 1.17 mmol, 3.0 equiv). The reaction was allowed to slowly warm to room temp. and stirred for 2 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in anh. THF (4 mL), 4-methylaniline (0.083 g, 0.78 mmol, 2.0 equiv) was added, and the resulting solution was stirred at room temp. for 14 h. The THF mixture was diluted with $CHCl_3$ (10 mL) and the resulting solution was washed with a 1N HCl solution (10 mL) and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient from hexane to 10% EtOAc/hexane) to give *N*-(2-carbo-1-prop-2-enyloxy-5-*tert*-butyl-3-thienyl)-*N'*-(4-methylphenyl)urea as a white solid (0.087 g, 60%): mp 52-62 °C, TLC (10% EtOAc/hexane) R_f0.34; ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 9H), 2.32 (s, 3H), 4.69 (app dt, *J*=5.5, 1.5 Hz, 2H), 5.25 (dd, *J*=10.3, 1.5 Hz, 1H), 5.35 (dd, *J*=16.9, 1.5 Hz, 1H), 5.87-5.98 (m, 1H), 7.13 (d, *J*=8.0 Hz, 2H), 7.30 (d, *J*=8.5 Hz, 2H), 7.88 (s, 1H), 9.68 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.8, 31.7 (3C), 35.2, 65.0, 104.9, 117.2, 118.2, 121.3 (2C), 129.7 (2C), 131.9, 134.0, 135.0, 146.1, 151.2, 164.3, 165.6; FAB-LRMS *m/z* (rel abundance) 373 (M + H, 13%).

Selected compounds synthesized using Method E:

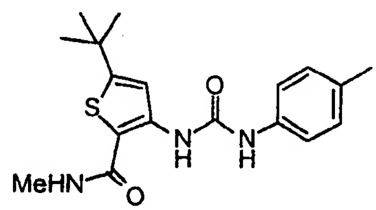
N-(2-(Carbo-2-propyloxy)-5-*tert*-butyl-3-thienyl)-*N'*-(4-methylphenyl)urea (Example 7): mp 72-86 °C, TLC (10% EtOAc/hexane) R_f0.34; ^{1}H NMR ($CDCl_3$) δ 1.28 (d, *J*=6.3 Hz, 3H), 1.35 (s, 9H), 2.31 (s, 3H), 5.11 (sept, *J*=6.3 Hz, 1H), 7.11 (d, *J*=8.1 Hz, 2H), 7.28 (d, *J*=8.1 Hz, 2H), 7.85 (s, 1H), 9.76 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.8, 21.9 (2C), 31.8 (3C), 35.2, 68.2, 105.6, 117.2, 121.2 (2C), 129.7 (2C), 133.8, 135.1, 145.7, 152.1, 163.9, 164.4; FAB-LRMS *m/z* (rel abundance) 375 (M + H, 70%).

N-(2-(Carbo-1-propyloxy)-5-*tert*-butyl-3-thienyl)-*N'*-(4-methylphenyl)urea (Example 53): mp 59-66 °C, TLC (10% EtOAc/hexane) ~~R_f0.38~~; ^{1}H NMR ($CDCl_3$) δ 0.96 (t, *J*=7.5 Hz, 3H), 1.35 (s, 9H), 1.69 (app hex, *J*=7.4 Hz, 2H), 2.31 (s, 3H), 4.14 (t, *J*=6.8 Hz, 2H),

7.11 (d, J=8.1 Hz, 2H), 7.29 (d, J=8.5 Hz, 2H), 7.86 (s, 1H), 9.71 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 10.3, 20.8, 22.0, 31.7 (3C), 35.2, 66.1, 105.3, 117.2, 121.2 (2C), 129.7 (2C), 133.9, 135.0, 145.7, 152.1, 164.2, 164.8; FAB-LRMS m/z (rel abundance) 375 (M + H, 36%).

Method F

Synthesis of *N*-(2-methylcarbamoyl-5-*tert*-butyl-3-thienyl)-*N'*-(4-methylphenyl)urea (Example 22).



Step 1

A solution of methyl 3-amino-5-*tert*-butylthiophene-2-carboxylate (20.0 g, 93.9 mmol), benzyl chloroformate (80.4 mL, 563 mmol), Na_2CO_3 (1.10 g, 9.93 mmol), toluene (400 mL) and water (50 mL) was heated at the reflux temp. for 18 h. Volatiles were removed under reduced pressure. The resulting oil was dissolved in EtOAc, washed with water and a concentrated NaCl solution, dried ($MgSO_4$) and concentrated under reduced pressure to afford methyl 3-(*N*-carbobenzyloxyamino)-5-*tert*-butylthiophene-2-carboxylate as a crude oil in quantitative yield.

Step 2

To a saturated solution of methylamine in MeOH (200 mL) in a screw top vessel was added methyl 3-(*N*-carbobenzyloxyamino)-5-*tert*-butylthiophene-2-carboxylate (13.6 g, 39.2 mmol) and NaCN (0.98 g, 20 mmol). The vessel was sealed and the reaction mixture was heated to 50 °C for 8 h. The resulting solution was poured into water (500 mL) and extracted with EtOAc. The organic layer was washed with water and a concentrated NaCl solution, dried (Na_2SO_4), and concentrated under reduced pressure. The crude material was purified by flash chromatography (EtOAc/hexane) affording *N*-methyl-3-(*N*-carbobenzyloxyamino)-5-*tert*-butylthiophene-2-carboxamide (2.76 g, 20%).

Step 3

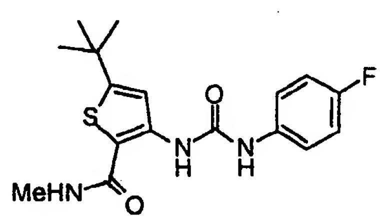
N-Methyl-3-(*N*-carbobenzyloxyamino)-5-*tert*-butylthiophene-2-carboxamide (2.76 g, 8 mmol) was dissolved in a 1:1 v/v solution of 48% HBr and AcOH (100 mL) and heated to 30 °C for 24 h. The acidic solution was cooled and adjusted to pH 4 with a saturated $NaHCO_3$ solution. Methylamine (4 mL, 2M in THF) was added and the resulting mixture was extracted with CH_2Cl_2. The organic phase was concentrated under reduced pressure to afford *N*-methyl-3-amino-5-*tert*-butylthienyl-2-carboxamide (0.092 g, 54%).

Step 4

A solution of the *N*-methyl-3-amino-5-*tert*-butylthiophene-2-carboxamide (0.60 g, 2.83 mmol) and 4-methylphenyl isocyanate (0.36 mL, 2.83 mmol) in toluene (2 mL) was heated at the reflux temp. for 18 h. The resulting solution was concentrated under reduced pressure and the resulting solid was purified by flash chromatography ($EtOAc/CH_2Cl_2$) affording *N*-(2-methylcarbamoyl-5-*tert*-butyl-3-thienyl)-*N'*-(4-methylphenyl)urea (0.42 g, 44%): mp 202-4 °C; ^1H NMR ($CDCl_3$) δ 1.38 (s, 9H), 2.31 (s, 3H), 2.91 (d, *J*=4.9 Hz, 3H), 5.59 (bs, 1H), 7.11 (d, *J*=8.5 Hz, 2H), 7.29 (d, *J*=8.5 Hz, 2H), 7.90 (s, 1H), 10.53 (s, 1H).

Method G

Synthesis of *N*-(2-methylcarbamoyl-5-*tert*-butyl-3-thienyl)-*N'*-(4-fluorophenyl)urea (Example 25).



Step 1

A slurry of methylamine hydrochloride (9.51 g, 141 mmol, 3.1 equiv) in anh. toluene (600 mL) at 0 °C was treated with $AlMe_3$ (2M in toluene, 70 mL, 141 mmol, 3.1 equiv) over 10 min. The resulting solution was stirred at 0 °C for 1 h then allowed to warm to

room temp. and stirred for 40 min. Methyl 3-amino-5-*tert*-butylthiophene-2-carboxylate (9.87 g, 46 mmol) was added to the aluminum amide solution. The resulting mixture was heated at the reflux temp. for 3 d, cooled to 0 °C, and a 6N HCl solution was added dropwise. The quenched mixture was made basic with a 20% KOH solution (95 mL). The resulting slurry was partitioned between H_2O (300 mL) and EtOAc (300 mL) and the aqueous layer was extracted with EtOAc (3 x 300 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to afford *N*-methyl-3-amino-5-*tert*-butylthiophene-2-carboxamide as a green-yellow solid (9.47 g, 97%): mp 230-1 °C; TLC (20% EtOAc/CH_2Cl_2) R_f 0.23; 1H NMR (d^6-DMSO) δ 1.28 (s, 9H), 2.63 (d, *J*=4.8 Hz, 3H), 6.29 (br s, 2H), 6.37 (d, *J*=1.1 Hz, 1H), 7.22 (q, *J*=4.0 Hz, 1H).

Step 2

A slurry of *N*-methyl-3-amino-5-*tert*-butylthiophene-2-carboxamide (7.63 g, 36 mmol) and 4-fluorophenyl isocyanate (4.93 g, 36 mmol, 1.0 equiv) in anh. toluene (100 mL) was heated at the reflux temp. for 3 h, during which the mixture clarified then generated a new precipitate, which was filtered while hot. The resulting solids were washed with hexane and dried under reduced pressure to afford *N*-(2-methylcarbamoyl-5-*tert*-butylthienyl)-*N'*-(4-fluorophenyl)urea (10.2 g, 81%): mp 203-4 °C; TLC (5% MeOH/CH_2Cl_2) R_f 0.61; ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 9H), 2.73 (d, *J*=4.4 Hz, 3H), 7.07-7.13 (m, 2H), 7.49-7.54 (m, 2H), 7.80 (s, 1H), 7.96 (q, *J*=4.4 Hz, 1H), 9.88 (s, 1H), 10.46 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.8, 31.6 (3C), 34.5, 107.4, 115.2 (d, J_{C-F}=22.0 Hz, 2C), 117.3, 120.1 (d, J_{C-F}=7.3 Hz, 2C), 136.1 (d, J_{C-F}=2.4 Hz, 2C), 143.1, 151.6, 157.4 (d, J_{C-F}=238.1 Hz, 1C), 158.0, 164.3; EI-LRMS *m/z* (rel abundance) 349 (M^+, 13%).

Selected compounds synthesized using Method G:

N-(2-Methylcarbamoyl-5-*tert*-butyl-3-thienyl)-*N'*-(4-ethylphenyl)urea (Example 23): mp 101-4 °C, TLC (20% EtOAc.hexane) R_f 0.18; ^{1}H NMR ($CDCl_3$) δ 1.20 (t, *J*=7.7 Hz, 3H), 1.20 (s, 9H), 2.59 (q, *J*=7.7 Hz, 2H), 2.88 (d, *J*=4.8 Hz, 3H), 5.64 (br d, J=4.4 Hz, 1H), 7.12 (d, *J*=8.1 Hz, 2H), 7.32 (d, *J*=8.5 Hz, 2H), ~~7.42~~ (br m, 1H), 7.90 (s, 1H), 10.54 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 15.6, 26.3, 28.2, 31.8 (3C), 35.0, 106.8, 118.1, 120.2 (2C),

128.3 (2C), 135.9, 139.5, 144.5, 152.1, 159.5, 165.6; FAB-LRMS *m/z* (rel abundance) 360 (M + H, 14%).

N-(2-Methylcarbamoyl-5-*tert*-butyl-3-thienyl)-*N'*-(4-isopropylphenyl)urea (Example 24): mp 113-20 °C, TLC (20% EtOAc.hexane) R_f 0.20; ^{1}H NMR (d^6-DMSO) δ 1.17 (d, *J*=7.0 Hz, 6H), 1.35 (s, 9H), 2.73 (d, *J*=4.4 Hz, 3H), 2.82 (sept, *J*=7.0 Hz, 1H), 7.13 (d, *J*=8.5 Hz, 2H), 7.41 (d, *J*=8.1 Hz, 2H), 7.80 (s, 1H), 7.93 (br q, *J*=4.8 Hz, 1H), 9.75 (s, 1H), 10.40 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 15.8 (2C), 25.9, 27.5, 31.6 (3C), 34.5, 107.3, 118.5 (2C), 127.8 (2C), 137.2, 137.5, 143.2, 151.6, 157.9, 164.3; FAB-LRMS *m/z* (rel abundance) 374 (M + H, 50%).

N-(2-Methylcarbamoyl-5-*tert*-butyl-3-thienyl)-*N'*-(2,4-dimethylphenyl)urea (Example 27): mp 195-6 °C; ^{1}H NMR (d^6-DMSO) δ 1.32 (s, 9H), 2.17 (s, 3H), 2.23 (s, 3H), 2.71 (d, *J*=4.4 Hz, 3H), 6.93 (br d, *J*=8.1 Hz, 1H), 6.98 (br s, 1H), 7.27 (d, *J*=8.1 Hz, 1H), 7.89 (q, *J*=4.0 Hz, 1H), 8.96 (s, 1H), 10.31 (s, 1H); EI-LRMS *m/z* (rel abundance) 359 (M^+, 7%).

N-(2-Methylcarbamoyl-5-*tert*-butyl-3-thienyl)-*N'*-(3-chloro-4-methylphenyl)urea (Example 28): mp 178-9 °C; ^{1}H NMR (d^6-DMSO) δ 1.31 (s, 9H), 2.24 (s, 3H), 2.72 (d, *J*=4.4 Hz, 3H), 7.19-7.24 (m, 2H), 7.73 (d, *J*=1.8 Hz, 1H), 7.79 (s, 1H), 7.97 (br q, *J*=4.3 Hz, 1H), 9.96 (s, 1H), 10.49 (s, 1H); EI-LRMS *m/z* (rel abundance) 379 (M^+, 30%), 381 (M^+ + 2, 14%).

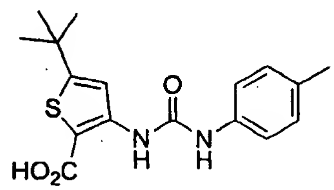
N-(2-Methylcarbamoyl-5-*tert*-butyl-3-thienyl)-*N'*-(3-fluoro-4-methylphenyl)urea (Example 29): mp 182-3 °C; ^{1}H NMR (d^6-DMSO) δ 1.32 (s, 9H), 2.13 (d, J_{F-H}=1.5 Hz, 3H), 2.70 (d, *J*=4.4 Hz, 3H), 7.08-7.12 (m, 2H), 7.42 (dd, *J*=1.8, 12.5 Hz, 2H), 7.76 (s, 1H), 7.95 (q, *J*=4.8 Hz, 1H), 9.94 (s, 1H), 10.45 (s, 1H) ; FAB-LRMS *m/z* (rel abundance) 364 (M + H, 10%).

N-(2-Methylcarbamoyl-5-*tert*-butyl-3-thienyl)-*N'*-(3-chloro-4-fluorophenyl)urea (Example 30): mp 203-4 °C; ^{1}H NMR (d^6-DMSO) δ 1.34 (s, 9H), 2.72 (d, *J*=4.4 Hz, 3H),

7.31-7.35 (m, 2H), 7.77 (s, 1H), 7.84 (dm, *J*=5.9 Hz, 1H), 7.99 br q, *J*=4.4 Hz, 1H), 10.06 (s, 1H), 10.54 (s, 1H); FAB-LRMS *m/z* (rel abundance) 359 (M + H, 52%), 386 (M+ 2 + H, 22%).

Method H

Synthesis of *N*-(2-carboxy-5-*tert*-butyl-3-thienyl)-*N'*-(4-methylphenyl)urea (Example 4).

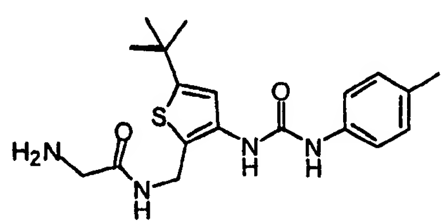


N-(2-Carbobenzyloxy-5-*tert*-butyl-3-thienyl)-*N'*-(4-methylphenyl)urea was synthesized as described in Method E.

To a solution of *N*-(2-carbobenzyloxy-5-*tert*-butyl-3-thienyl)-*N'*-(4-methylphenyl)urea (0.19 g, 0.40 mmol) in EtOH (19 mL) was added 10% Pd/C (0.010 g). The resulting suspension was treated with H_2 (52 psi) in a Parr® shaker for 18 h. The slurry was filtered through a pad of Celite® and concentrated under reduced pressure to afford *N*-(2-carboxy-5-*tert*-butyl-3-thienyl)-*N'*-(4-methylphenyl)urea (0.12 g, 90%):^{1}H NMR (d^6-DMSO) δ 13 (s, 9H), 2.2 (s, 3H), 7.1 (d, 2H), 7.4 (d, 2H), 7.8 (s, 1H); FAB-LRMS *m/z*) 333 (M + H).

Method I

Synthesis of *N*-(2-(*N*-glycylaminomethyl)-5-*tert*-butyl-3-thienyl)-*N'*-(4-methylphenyl)urea (Example 51).



Step 1

N-(2-Carbamoyl-5-*tert*-butyl-3-thienyl)-*N'*-(4-methylphenyl)urea was synthesized in a manner analogous to that described in Method F.

To a solution of $BH_3 \cdot THF$ (1.8 mL, 1M in THF) was added a solution of *N*-(2-carbamoyl-5-*tert*-butyl-3-thienyl)-*N'*-(4-methylphenyl)urea in THF (3 mL) and the resulting mixture was heated under reflux for 48 h. After cooling to room temp., a concentrated hydrochloric acid solution was added, and the resulting mixture was extracted with EtOAc. The organic layer was washed with a saturated Na_2CO_3 solution, and a saturated NaCl solution, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by chromatography (SiO_2, 0.1% NH_4OH/10% MeOH/CH_2Cl_2 to afford *N*-(2-aminomethyl-5-*tert*-butyl-3-thienyl)-*N'*-(4-methylphenyl)urea (0.18 g, 85 %): ^1H NMR ($CDCl_3$) δ 1.38 (s, 9H), 2.34 (s, 3H), 3.81 (s, 2H), 6.72 (s, 1H), 7.29 (d, *J*=8.6 Hz, 2H), 7.16 (d, *J*=8.5 Hz, 2H), 7.87 (s, 1h); FAB-LRMS *m/z* 318 (M + H).

Step 2

To a solution of *N*-(2-aminomethyl-5-*tert*-butyl-3-thienyl)-*N'*-(4-methylphenyl)urea (0.20 g, 0.63 mmol) and *N*-carbo-*tert*-butoxyglycine (0.11 g, 0.63 mmol, 1.0 equiv) in THF (2 mL) at room temp. were added dicyclohexylcarbodiimide (0.13 g, 0.63 mmol, 1.0 equiv) and 1-hydroxybenzotriazole monohydrate (0.008 g, 0.06 mmol, 10 mol%). The resulting mixture was allowed to stir 18 h, diluted with EtOAc (5 mL), and washed with a saturated NaCl solution. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient from 30% EtOAc/hexane to 50% EtOAc/hexane) to afford *N*-(2-(*N*-(*N*-carbo-*tert*-butoxyglycyl)aminomethyl)-5-*tert*-butyl-3-thienyl)-*N'*-(4-methylphenyl)urea (0.12 g, 40%, Example 52): mp 174-176 °C; ^1H NMR ($CDCl_3$) δ 1.38 (s, 9H), 2.27 (m, 3H), 4.38 (m, 2H), 6.67 (bs, 1H), 6.89 (m, 1H), 7.27 (m, 1H), 7.33 (m, 2H), 8.58 (bs, 1H); FAB-LRMS *m/z* 475 (M + H).

Step 3

To a solution of *N*-(2-(*N*-(*N*-carbo-*tert*-butoxyglycyl)aminomethyl)-5-*tert*-butyl-3-thienyl)-*N'*-(4-methylphenyl)urea (0.050 g, 0.105 mmol) in CH_2Cl_2 (3 mL) at room temp. was added trifluoroacetic acid (0.50 mL, 6.49 mmol, 62 equiv). The resulting mixture

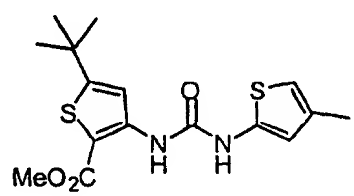
was stirred for 3 h, washed with a saturated $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (for CH_2Cl_2 to 20% $MeOH/CH_2Cl_2$) to give *N*-(2-(*N*-glycylaminomethyl)-5-*tert*-butyl-3-thienyl)-*N'*-(4-methylphenyl)urea (0.019 g, 48%): mp 93-6 °C; ^1H NMR ($CDCl_3$) δ 1.14 (s, 9H), 2.08 (s, 3H), 3.89 (s, 2H), 4.34 (br s, 7H), 6.67 (s, 1H), 6.87 (d, *J*=8.1 Hz, 2H), 7.12 (d, *J*=8.5 Hz, 2H), 7.3 (m, 2H).

Selected compound synthesized using Method I:

N-(2-(*N*-Acetylaminomethyl)-5-*tert*-butyl-3-thienyl)-*N'*-(4-methylphenyl)urea (Example 50): mp 203-5 °C; ^1H NMR ($CDCl_3$/d^6-DMSO) δ 1.3 (s, 9H), 1.9 (s, 3H), 2.2 (s, 3H), 4.3 (d, 2H), 7.0 (d, 2H), 7.2 (s, 1H), 7.3 (m, 2H), 8.6 (br s, 1H); FAB-LRMS *m/z* 360 (M + H).

Method J

Synthesis of *N*-(2-carbomethoxy-5-*tert*-butyl-3-thienyl)-*N'*-(4-methyl-2-thienyl)urea (Example 15).



Step 1

A solution of 3-methylthiophene (5 mL, 51.75 mmol), sodium persulfate (18.48 g, 77.6 mmol) and palladium acetate (5.81 g, 25.88 mmol) in acetic acid (500 mL) was heated to the reflux temp. A slow stream of carbon monoxide was bubbled through the solution for 3 h. The reaction was cooled to 20 °C and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2. Celite® was added and the solution was filtered, then passed through a pad of silica gel, and concentrated under reduced pressure. The residue was dissolved in EtOAc and extracted with a 2N KOH solution. The aqueous layer was washed with EtOAc, the pH was adjusted to zero with a concentrated HCl solution, and the resulting mixture was extracted with EtOAc. The organic layer was washed with a

saturated NaCl solution and concentrated under reduced pressure to yield a mixture of 3-methylthiophene-2-carboxylic acid and 4-methylthiophene-2-carboxylic acid (1.86 g, 25%).

Step 2

To a solution of a mixture of 3-methylthiophene-2-carboxylic acid and 4-methylthiophene-2-carboxylic acid (1.11 g, 7.81 mmol) and triethylamine (1.3 mL, 9.38 mmol) in acetone (75 mL) at -15 °C was slowly added ethyl chloroformate (1.12 mL, 11.72 mmol). The acetone solution was stirred for 15 min and a solution of NaN_3 (0.86 g, 13.3 mmol) in water (15 mL) was added. The reaction was stirred for 30 min, then diluted with CH_2Cl_2 and washed with a 1:1 v/v mixture of a saturated NaCl solution and water. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexane) to give a mixture of azidoesters (0.91 g, 70%) which were used in the next step without further purification.

Step 3

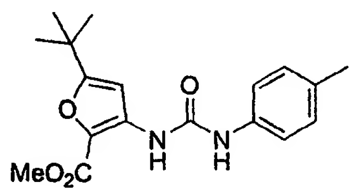
The azidoester mixture (0.120 g, 0.72 mmol) was dissolved in toluene (3 mL) and heated to 100 °C for 5 h, then cooled to 20 °C. Methyl 3-amino-5-*tert*-butylthiophene-2-carboxylate (0.11 g, 0.50 mmol) was added and the reaction was heated to 95 °C for 18 h. The reaction was cooled to 20 °C and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexane) followed by normal phase HPLC (CH_2Cl_2), to afford *N*-(2-carbomethoxy-5-*tert*-butyl-3-thienyl)-*N'*-(4-methyl-2-thienyl)urea (0.082 g, 46%) and *N*-(2-carbomethoxy-5-*tert*-butyl-3-thienyl)-*N'*-(3-methyl-2-thienyl)urea (0.018 g, 10%). *N*-(2-Carbomethoxy-5-*tert*-butyl-3-thienyl)-*N'*-(3-methyl-2-thienyl)urea: ^1H NMR ($CDCl_3$) δ 1.35 (s, 9H), 2.15 (s, 3H), 3.75 (s, 3H), 6.45 (bs, 2H), 6.85 (d, 1H), 7.10 (d, 1H), 7.85 (s, 1H), 9.70 (s, 1H), FAB-LRMS *m/z* (rel abundance) 353 (M + H, 88%). *N*-(2-Carbomethoxy-5-*tert*-butyl-3-thienyl)-*N'*-(4-methyl-2-thienyl)urea: ^1H NMR ($CDCl_3$) δ 1.35 (s, 9H), 2.20 (s, 3H), 3.75 (s, 3H), 6.55 (bs, 2H), 7.80 (br s, 1H), 7.85 (s, 1H), 9.80 (s, 1H); FAB-LRMS *m/z* (rel abundance) 353 (M + H, 30%).

Selected compound synthesized using Method J:

N-(2-Carbomethoxy-5-*tert*-butyl-3-thienyl)-*N'*-(5-methyl-2-thienyl)urea (Example 14): mp 118-20 °C; ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 9H), 2.40 (s, 3H), 3.75 (s, 3H), 6.55 (bs, 2H), 7.90 (s, 1H), 8.10 (bs, 1H), 9.75 (s, 1H); FAB-LRMS *m/z* (rel abundance) 353 (M + H, 56%).

Method K

Synthesis of *N*-(2-carbomethoxy-5-*tert*-butyl-3-furyl)-*N'*-(4-methylphenyl)urea (Example 32).



Step 1

To a solution of 2-*tert*-butylfuran (4.5 g, 36 mmol) in anh. THF (60 mL) at -78 °C under N_2 was added *n*-butyllithium (1.6M in hexane, 25 mL, 40 mmol, 1.1 equiv) dropwise. After 30 min, the cooling bath was replaced with an ice bath and the mixture was stirred at 0 °C for 1 h. Dry CO_2, generated from dry ice and dried over an anhydrous Na_2SO_4 tower, was bubbled into the reaction mixture over 20 min at -78 °C and then at 0 °C. The reaction mixture was acidified to pH 1 with a 1M HCl solution, then extracted with EtOAc. The organic layer was washed with a concentrated NaCl solution, dried ($NaSO_4$) and concentrated under reduced pressure to give 5-*tert*-butylfuran-2-carboxylic acid as a pale yellow solid (4.2 g, 69%): ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 9H), 6.11 (d 1H, $J = 3.3$ Hz), 7.19 (d, 1H, $J = 3.3$ Hz), 11.0 (br s, 1H).

Step 2

A solution of 5-*tert*-butylfuran-2-carboxylic acid (2.0 g, 11.9 mmol) in anh. THF (30 mL) was cooled to -78 °C under N_2, then *n*-butyllithium (1.6M in hexane solution, 15.6 mL, 25 mmol, 2.1 equiv) was added dropwise. After 30 min, TsN_3 (2.3 g, 11.9 mmol, 1.1

equiv) in anh. THF (3 mL) was added dropwise via cannula followed by a wash portion of anh. THF (3 mL). The yellow solution was allowed to warm to 0 °C over 2 h, then 6 g of KOAc (6 g, 60 mmol, 5 equiv) was added and the suspension was stirred rapidly at room temp. for 14 h. The mixture was diluted with Et_2O and extracted with water. The aqueous phase was acidified to pH 1 with a 1M HCl solution, then extracted thoroughly with EtOAc. The organic phase was washed with a concentrated NaCl solution, dried ($NaSO_4$), and concentrated under reduced pressure. The resulting red oil was diluted with Et_2O (150 mL) and MeOH (20 mL) then treated with $TMSCHN_2$ (2.0M in hexane, 45 mL, 90 mmol). After 30 min, the mixture was concentrated, and the oil was purified by flash chromatography (10% EtOAc/hexane) to give a colorless oil (1.72 g). Analysis of the product by ^1H NMR indicated an approximately 2:3 mixture of methyl 3-azido-5-*tert*-butylfuran-2-carboxylate and methyl 5-*tert*-butylfuran-2-carboxylate, which co-elute. Methyl 3-azido-5-*tert*-butylfuran-2-carboxylate: ^1H NMR ($CDCl_3$) δ 1.25 (s, 9H), 3.80 (s, 3H), 5.99 (s, 1H); FTIR (neat) 2965 (s), 2118 (s), 1723 (s) cm^{-1}. The mixture was used in the next step without further purification.

Step 3

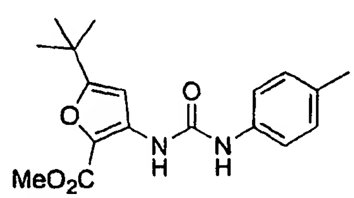
A mixture of methyl 3-azido-5-*tert*-butylfuran-2-carboxylate and methyl 5-*tert*-butylfuran-2-carboxylate (1.72 g) and 10% Pd/C (0.50 g) in cellosolve (30 mL) was successively evacuated and purged with H_2 three times. The reaction mixture was then shaken under H_2 (40 psi) for 1 h, diluted with EtOAc and filtered through a pad of Celite®. The filtrate was concentrated under reduced pressure, then purified by flash chromatography (20% EtOAc/ hexane) to give methyl 5-*tert*-butylfuran-2-carboxylate (0.73 g, 34%) followed by methyl 3-amino-5-*tert*-butylfuran-2-carboxylate (0.59 g, 25% yield from 5-*tert*-butylfuran-2-carboxylic acid). Methyl 3-amino-5-*tert*-butylfuran-2-carboxylate: ^1H NMR ($CDCl_3$) δ 1.29 (s, 9H), 4.24 (br s, 2H), 5.76 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.3, 32.8, 50.5, 98.3, 124.1, 144.9 (br), 160.5, 168.1, 178.7; FTIR (neat) 3330-2950 (br, s), 2850 (m), 1680 (s), 1637 (s), 1537 (s), 1346 (s), 1131 (s) cm^{-1}.

Step 4

Phosgene (1.93M in toluene, 1.3 mL, 2.5 mmol, 10 equiv) was added rapidly to a solution of methyl 3-amino-5-*tert*-butylfuran-2-carboxylate (0.050 g, 0.25 mmol) and anh. pyridine (1.0 mL) in anh. toluene (5mL) at room temp. After 30 min, the orange suspension was concentrated under reduced pressure, then successively charged with dry toluene (1 mL) and concentrated (2x). Finally, anh. toluene (3 mL) was added followed by *p*-toluidine (0.100 g, 0.93 mmol, 3.7 equiv). The orange mixture was stirred overnight, diluted with EtOAc, washed with a 1M HCl solution and a concentrated NaCl solution, then dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography to give *N*-(2-carbomethoxy-5-*tert*-butyl-3-furyl)-*N'*-(4-methylphenyl)urea (0.080 g, 96%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 9H), 2.30 (s, 3H), 3.77 (s, 3H), 7.02 (s, 1H), 7.11 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 7.87 (br s, 1H), 8.68 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.6, 28.3 (3C), 33.0, 51.0, 100.1, 121.4 (2C), 126.0, 129.5 (2C), 134.0, 134.8, 137.7, 152.5, 160.5, 168.2; FTIR (neat) 3400-3200 (br, m), 2966 (s), 1676 (s), 1622 (s), 1536 (s), 1306 (s), 1097 (m) cm^{-1}.

Method L-1

Synthesis of *N*-(2-carbomethoxy-5-*tert*-butyl-3-furyl)-*N'*-(4-methylphenyl)urea (Example 32).



Step 1

3-Chloro-4,4-dimethyl-2-pentenenitrile was prepared following a literature procedure (Hatcher et al. *J. Heterocycl. Chem.* **1989**, *26*, 1575). $POCl_3$ (22.4 mL), 0.24 mol, 2.4 equiv) was slowly added to a 0 °C solution of DMF (20.2 mL, 0.26 mol, 2.6 equiv) keeping the temp. under 20 °C. The resulting pink solid was heated to 40 °C, pinacolone (12.5 mL, 0.10 mol) was added to the resulting red solution, and this mixture was heated to 55 °C for 2 h and 75 °C for 2 h. $NH_2OH \cdot HCl$ (~~16.7~~ g, 0.24 mol, 2.4 equiv) was added to the 75 °C mixture slowly (<100 mg portions; CAUTION gas evolution and foaming).

The resulting solution was heated to 85 °C for 2 h, then allowed to cool to room temp. overnight. The resulting yellow gel was separated between H_2O (500 mL) and EtOAc (300 mL). The aqueous layer was extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with a saturated NaCl solution, dried (Na_2SO_4) and concentrated under reduced pressure to give 3-chloro-4,4-dimethyl-2-pentenenitrile as a brown oil (13.2 g, 93%): ^{1}H NMR ($CDCl_3$) δ 1.23 (s, 9H), 5.56 (s, 1H); GC-LRMS *m/z* (rel abundance) 143 (28%), 145 (11%). This material was used in the next step without further purification.

Step 2

To a slurry of NaH (5.98 g, 0.24 mol, 2.6 equiv) in anh. DME (800 mL) at 0 °C was added methyl glycolate (23.0 g, 0.26 mol, 2.8 equiv) over 20 min. The mixture was stirred for 1 h at room temp. and a solution of 3-chloro-4,4-dimethyl-2-pentenenitrile (13.1 g, 0.091 mol) in DME (100 mL) was added. The resulting solution was heated to 85 °C for 42 h, cooled to room temp., and treated with H_2O (100 mL). The resulting mixture was separated between H_2O (200 mL) and EtOAc (300 mL). The aqueous layer was extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with a saturated NaCl solution, dried (Na_2SO_4), and concentrated under reduced pressure. The residual oil was purified by flash chromatography (300 g SiO_2, gradient from 50% CH_2Cl_2/hexane to 20% EtOAc/CH_2Cl_2) to give methyl 3-amino-5-*tert*-butylfuran-2-carboxylate as a yellow solid (2.98 g, 17%): mp 91-2 °C; TLC (20% EtOAc/hexane) R_f 0.36; ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 9H), 3.84 (s, 3H), 4.54 (br s, 2H), 5.75 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.5 (3C), 33.0, 50.7, 98.5, 128.8, 131.0, 160.7, 168.3.

Step 3

To a solution of phosgene (1.93M in toluene, 9.7 mL, 18.6 mmol, 3.0 equiv) in CH_2Cl_2 (80 mL) at 0 °C was added a solution of methyl 3-amino-5-*tert*-butylfuran-2-carboxylate (1.23 g, 6.2 mmol) and pyridine (1.97 g, 24.9 mmol, 4.0 equiv) in CH_2Cl_2 (20 mL). The reaction mixture was allowed to slowly warm to room temp. and rapidly form a precipitate. The resulting slurry was stirred at room temp. for 1 h, then concentrated

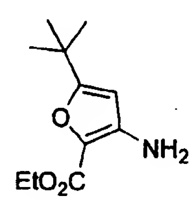
under reduced pressure to give 2-carbomethoxy-5-*tert*-butyl-3-furyl isocyanate and pyridinium hydrochloride. 2-Carbomethoxy-5-*tert*-butyl-3-furyl isocyanate: ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 9H), 4.85 (s, 3H), 5.90 (s, 1H). The mixture was used in the next step without further puiirification.

Step 4

The 2-carbomethoxy-5-*tert*-butyl-3-furyl isocyanate prepared in Step 3 was dissolved in anh. toluene (40 mL), *p*-toluidine (2.05 g, 6.02 mmol, 1.0 equiv) was added, and the resulting solution was stirred at room temp. for 1 h. The toluene mixture was concentrated under reduced pressure, then diluted with $CHCl_3$ (150 mL). The organic solution was washed with a 1N HCl solution (2 x 100 mL) and a saturated NaCl solution (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (100 g SiO_2, gradient from hexane to 10% EtOAc/hexane) to give *N*-(2-carbomethoxy-5-*tert*-butyl-3-furyl)-*N'*-(4-methylphenyl)urea as a yellow solid (0.71 g, 35): mp 78-9 °C; TLC (20% EtOAc/hexane) R_f 0.46; ^{1}H NMR δ 1.28 (s, 9H), 2.33 (s, 3H), 3.80 (s, 3H), 7.03 (s, 1H), 7.10 (br s, 1H), 7.15 (d, *J*=8.5 Hz, 2H), 7.27 (d, *J*=8.5 Hz, 2H) 8.60 (brs, 1H); ^{13}C NMR δ 20.8, 28.5 (3C), 33.2, 51.3, 100.3, 121.7 (br s, 2C), 126.2, 129.8 (br s, 2C), 134.3 (br s), 135.0, 137.5 (br s), 152.6, 160.8, 168.5; FAB-LRMS *m/z* (rel abundance) 331 (M + H, 64%).

Method L-2

Synthesis of ethyl 3-amino-5-*tert*-butylfuran-2-carboxylate.



Step 1

A 0 °C solution of triphenylphosphine (2.72 g, 10.4 mmol, 1.3 equiv) in anh. THF (50 mL) was treated with diethyl azodicarboxylate (1.81 g, 10.4 mmol, 1.3 equiv), ethyl

glycolate (1.08 g, 10.4 mmol, 1.3 equiv) and 4,4-dimethyl-3-oxopentanenitrile (1.00 g, 8.0 mmol). The resulting solution was allowed to warm to room temperature, stirred for 15 h and concentrated under reduced pressure. The residue was purified by flash chromatography (11 cm x 22 cm SiO_2, gradient from 5% EtOAc/hex to 8% EtOAc/hex) to afford *(Z)*-4,4-dimethyl-3-(ethoxycarbonylmethoxy)pentenenitrile (1.36 g, 80%) as a colorless oil: TLC (5% EtOAc/hexanes) R_f 0.26; ^1H NMR ($CDCl_3$) δ 1.12 (s, 9H), 1.28 (t, J = 7.0 Hz, 3H), 4.24 (q, J = 7.0 Hz, 2H), 4.55 (s, 1H), 5.00 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 13.9, 27.8, 38.2, 61.5, 67.1, 67.3, 117.0, 167.1, 180.7; CI-LRMS *m/z* (rel abundance) 212 (M+H, 100%). Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.57; H, 7.90; N, 6.47.

Step 2

To a slurry of sodium hydride (62 mg, 2.6 mmol, 1.1 equiv) in anh. THF (50 mL) was added *(Z)*-4,4-dimethyl-3-(ethoxycarbonylmethoxy)pentenenitrile (0.50 g, 2.4 mmol). The reaction mixture was stirred for 3 h, treated with a saturated aq. NH_4Cl solution (2 mL), and concentrated under reduced pressure. The residue was purified by flash chromatography (50 g SiO_2, 10% EtOAc/hex) to afford ethyl 3-amino-5-*tert*-butylfuran-2-carboxylate (0.44 g, 88%) as a white solid: mp 44-45 °C; TLC (10% EtOAc/hex) R_f 0.19; ^1H NMR ($CDCl_3$) δ 1.26 (s, 9H), 1.36 (t, J = 7.0 Hz, 3H), 4.32 (q, J = 7.0 Hz, 2H), 4.51 (br s, 2H), 5.75 (s, 1H); FAB-LRMS *m/z* (rel abundance) 212 (M+H, 100%). Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.48; H, 8.06; N, 6.61.

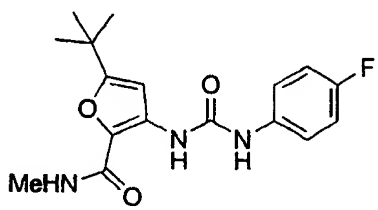
Selected compound synthesized using Method L-1 or L-2:

N-(2-Carbomethoxy-5-*tert*-butyl-3-furyl)-*N'*-(4-fluorophenyl)urea (Example 33): mp 81-2 °C; TLC (20% EtOAc/hexane) R_f 0.37; ^1H NMR δ 1.28 (s, 9H), 3.82 (s, 3H), 6.99 (s, 1H), 7.04 (app td, J=8.6, 2.2 Hz, 2H), 7.30-7.39 (m, 2H), 8.63 (brs, 1H); ^{13}C NMR δ 28.5 (3C), 33.3, 51.4, 100.2, 116.0 (d, $J_{C\text{-}F}$=22.0 Hz, 2C), 123.0 (br d, $J_{C\text{-}F}$=4.9 Hz, 2C), 126.3, 133.5 (d, $J_{C\text{-}F}$=3.7 Hz, 1C), 152.3, 159.8 (d, $J_{C\text{-}F}$=242.9 Hz, 1C), 168.6; FAB-LRMS *m/z* (rel abundance) 335 (M + H, 60%).

N-(2-Carbomethoxy-5-*tert*-butyl-3-furyl)-*N'*-(2,3-dichlorophenyl)urea (Example 34): mp 195-7 °C; TLC (20% EtOAc/hexane) R_f 0.58; ^{1}H NMR δ 1.31 (s, 9H), 3.89 (s, 3H), 6.99 (s, 1H), 7.20-7.22 (m, 2H), 7.29 (s, 1H), 8.08 (dd, *J*=6.4, 3.5 Hz, 1H) 8.76 (brs, 1H); ^{13}C NMR δ 28.5 (3C), 33.3, 51.5, 100.1, 113.3, 119.7, 125.0, 126.5, 127.6, 132.9, 136.4, 137.5, 150.9, 161.1, 168.5; EI-LRMS *m/z* (rel abundance) 385 (M^+, 100%), 387 (M^+ + 2, 71%), 389 (M^+ + 4, 13%).

Method M

Synthesis of *N*-(2-methylcarbamoyl-5-*tert*-butyl-3-furyl)-*N'*-(4-fluorophenyl)urea (Example 36).



Step 1

A slurry of methylamine hydrochloride (1.03 g, 15.2 mmol, 3.0 equiv) in anh. toluene (60 mL) at 0 °C was treated with $AlMe_3$ (2M in toluene, 7.6 mL, 15.2 mmol, 3.0 equiv). The resulting solution was stirred at 0 °C for 30 min and allowed to warm to room temp for 40 min. To the aluminum amide solution was then added methyl 3-amino-5-*tert*-butyl-2-furancarboxylate (1.00 g, 5.1 mmol). The resulting mixture was heated at the reflux temp. for 20 h, cooled to room temp., and a 6N HCl solution was added dropwise. The quenched mixture was made basic with a 1N NaOH solution (approximately 100 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with a saturated NaCl solution, dried (Na_2SO_4), and concentrated under reduced pressure to afford *N*-methyl-3-amino-5-*tert*-butyl-2-furancarboxamide as a yellow solid (0.90 g, 91%): TLC (20% EtOAc/CH_2Cl_2) R_f 0.26; ^{1}H NMR ($CDCl_3$) δ 1.23 (s, 9H), 2.93 (d, *J*=4.8 Hz, 3H), 4.51 (br s, 1H), 5.73 (s, 1H).

Step 2

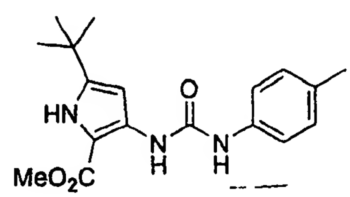
To a solution of *N*-methyl-3-amino-5-*tert*-butylfuran-2-carboxamide (0.15 g, 0.76 mmol) in anh. toluene (2 mL) at the reflux temp. was slowly added 4-fluorophenyl isocyanate (0.10 g, 0.76 mmol, 1.0 equiv). The resulting solution was allowed to stir at the reflux temp. for 14 h, cooled to room temp., and concentrated under reduced pressure. The residue was purified by flash chromatography (15 g SiO_2, gradient from 50% CH_2Cl_2/hexane to 100% CH_2Cl_2, then to 20% EtOAc/CH_2Cl_2) to afford *N*-(2-methylcarbamoyl-5-*tert*-butylfuryl)-*N'*-(4-fluorophenyl)urea (0.16 g, 61%): mp 109-11 °C, TLC (30% EtOAc/CH_2Cl_2) R_f 0.21; ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 9H), 2.89 (d, J=4.8 Hz, 3H), 6.02 (br q, J=4.8 Hz, 1H), 6.98 (app td, J=16.6, 4.1 Hz, 2H), 7.01 (s, 1H), 7.34-7.39 (m, 2H), 8.05 (br s, 1H), 9.14 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.5, 28.7 (3C), 33.1, 100.7, 115.6 (d, J_{C-F}=23.2 Hz, 2C), 121.5 (d, J_{C-F}=7.3 Hz, 2C), 128.3, 134.5 (br s), 152.4, 158.9 (d, J_{C-F}=242.9 Hz, 1C), 161.6, 165.8; FAB-LRMS *m/z* (rel abundance) 334 (M + H, 100%).

Selected compound synthesized using Method M:

N-(2-Methylcarbamoyl-5-*tert*-butylfuryl)-*N'*-(4-methylphenyl)urea (Example 35): mp 190-3 °C; TLC (30% EtOAc/CH_2Cl_2) R_f 0.25; ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 9H), 2.30 (s, 3H), 2.92 (d, J=4.8 Hz, 3H), 5.99 (br q, J=4.8 Hz, 1H), 7.03 (d, J=1.1 Hz, 1H), 7.10 (d, J=8.5 Hz, 2H), 7.29 (d, J=8.5 Hz, 2H),7.56 (br s, 1H), 9.12 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.8, 25.4, 28.7 (3C), 33.8, 100.7, 120.1 (2C), 128.4, 129.7 (2C), 133.1, 134.5, 135.7, 152.3, 161.6, 165.6; FAB-LRMS *m/z* (rel abundance) 330 (M + H, 100%).

<u>Method N-1</u>

Synthesis of *N*-(2-carbomethoxy-5-*tert*-butyl-3-pyrrolyl)-*N'*-(4-methyl-phenyl)urea (Example 38).



Step 1

To a solution of pyrrole-2-carboxylic acid (6.28 g, 56.5 mmol) in anh. MeOH (100 mL) under N_2 at room temp. was added TMSCl (17.9 mL, 141 mmol, 2.5 equiv) in one portion. After stirring overnight, the reaction mixture was concentrated under reduced pressure, redissolved in CH_2Cl_2, washed with water, dried (Na_2SO_4) and concentrated to give methyl pyrrole-2-carboxylate as a tannish semi-crystalline solid (4.62 g, 65%): ^{1}H NMR ($CDCl_3$) δ 3.86 (s, 3H), 6.29 (br q, 1H), 6.92 (br m, 1H), 6.96 (br m, 1H), 9.30 (br s, 1H). This material was used in the next step without further purification.

Step 2

To a solution of methyl pyrrole-2-carboxylate (0.30 g, 2.42 mmol) in anh. 1,2-dichloroethane (12 mL) under N_2 at room temp. was added $AlCl_3$ (0.710 g, 5.33 mmol, 2.2 equiv) in one portion. 2-Chloro-2-methylpropane (0.26 mL, 2.42 mmol, 1.0 equiv) was added in one portion via syringe. After 2 h, the reaction was quenched by slowly pouring it into a saturated $NaHCO_3$ solution. The resulting white suspension was extracted with Et_2O (2x). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give an off-white solid (0.40 g), which was purified by flash chromatography (60% CH_2Cl_2/hexane) to give methyl 5-*tert*-butylpyrrole-2-carboxylate as a white amorphous solid (0.36 g, 81%): ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 3.83 (s, 3H), 6.00 (t, J = 3.3 Hz, 1H), 6.81 (t, J = 3.3 Hz, 1H), 8.82 (br s, 1H).

Step 3

To a heterogeneous mixture of methyl 5-*tert*-butylpyrrole-2-carboxylate (1.65 g, 9.10 mmol) in concentrated H_2SO_4 (19 mL) under N_2 at room temp. was added fuming nitric acid (0.57 mL, 13.6 mmol, 1.5 equiv) in one portion via syringe. After 1 h, the reaction mixture was poured into ice-water and the resulting mixture was carefully adjusted to pH 7 with solid Na_2CO_3. The resulting mixture was extracted with Et_2O (2x), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified using flash chromatography (70% CH_2Cl_2/hexane) to give methyl 5-*tert*-butyl-3,4-dinitropyrrole-2-carboxylate (0.27 g) followed by methyl 5-*tert*-butyl-3-nitropyrrole-2-carboxylate (0.44

g). Resubmission of mixed fractions to the flash chromatography conditions provided additional methyl 5-*tert*-butyl-3-nitropyrrole-2-carboxylate (0.22 g, 0.66 g total, 32% total yield). Methyl 5-*tert*-butyl-3-nitropyrrole-2-carboxylate: ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 9H), 3.93 (s, 3H), 6.56 (d, J = 3.3 Hz, 1H), 9.22 (br s, 1H). Methyl 5-*tert*-butyl-3,4-dinitropyrrole-2-carboxylate: ^{1}H NMR ($CDCl_3$) δ 1.52 (s, 9H), 3.91 (s, 3H), 9.17 (br s, 1H).

Step 4

A mixture of methyl 5-*tert*-butyl-3-nitropyrrole-2-carboxylate (0.014 g, 0.062 mmol) and 10% Pd/C (3 mg) in dry MeOH (1 mL) was successively evacuated and purged with H_2 three times, then shaken under an atmosphere of H_2 (35 psi) for 1 h, diluted with CH_2Cl_2 and filtered through a pad of Celite®. The filtrate was concentrated under reduced pressure to give methyl 3-amino-5-*tert*-butylpyrrole-2-carboxylate as a bright yellow oil (0.012 g, 100%). ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 9H), 3.82 (s, 3H), 5.52 (d, J = 2.8 Hz, 1H), 7.89 (br s, 2H). This material was used in the next step without further purification.

Step 5

To a solution of methyl 3-amino-5-*tert*-butylpyrrole-2-carboxylate (12 mg, 0.062 mmol) and anh. pyridine (0.25 mL, 3.06 mmol, 49.4 equiv) in anh. toluene (1 mL) was rapidly added phosgene (1.93M in toluene, 0.32 mL, 0.62 mmol, 10 equiv). After 30 min, the orange suspension was concentrated under reduced pressure, then successively charged with anh. toluene (1 mL) and concentrated (2x). Finally, toluene (2 mL) was added followed by *p*-toluidine (10 mg, 0.094 mmol). The mixture was heated at 90 °C for 3 h, then was concentrated under reduced pressure. The residue was purified by preparative TLC (2 plates, 20 x 20 cm x 0.25 mm, 2% MeOH/CH_2Cl_2). The major UV-active band was isolated and the product was extracted from the silica using 5% MeOH/CH_2Cl_2 to give *N*-(2-carbomethoxy-5-*tert*-butyl-3-pyrrolyl)-*N'*-(4-methylphenyl)urea as a pale yellow amorphous solid (0.016 g, 80%): ^{1}H NMR (d^6-DMSO) δ 1.23 (s, 9H), 2.20 (s, 3H), 3.78 (s, 3H), 6.54 (d, J=3.0 Hz, 1H), 7.04 (d, J=8.5 Hz, 2H), 7.32 (d, J=8.5 Hz, 2H),

8.61 (s, 1H), 9.51 (s, 1H), 10.85 (br d, J=2.2 Hz, 1H); ^{13}C NMR (MeOD, $CDCl_3$, partial spectrum) δ 19.7, 29.0 (3C), 31.5, 50.0, 97.4, 105.9, 119.6 (2C), 128.9 (2C), 132.2, 136.2, 147.6, 153.5, 161.9; FTIR (KBr) 3341 (s), 2947 (m), 1676 (s), 1583 (s), 1548 (s), 1456 (s), 1279 (s), 1208 (s), 1094 (s); cm^{-1}; FAB-LRMS *m/z* (rel abundance) 330 (M+H, 47%).

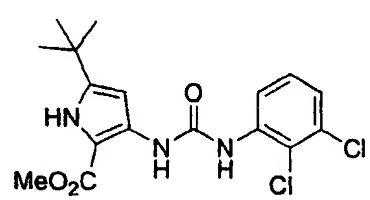
Selected compounds synthesized using Method N-1:

N-(2-Carbomethoxy-5-*tert*-butyl-3-pyrrolyl)-*N'*-(phenyl)urea (Example 37): ^{1}H NMR (d^6-DMSO) δ 1.23 (s, 9H), 3.78 (s, 3H), 6.54 (d, J=2.9 Hz, 1H), 7.26 (dd, J=2.6, 8.8 Hz, 1H), 7.48 (d, J=8.8 Hz, 1H), 7.90 (d, J=2.6 Hz, 1H), 8.76 (s, 1H), 9.97 (s, 1H), 10.95 (br d, J=1.8 Hz, 1H); FAB-LRMS *m/z* (rel abundance) 384 (M+H, 93%).

N-(2-Carbomethoxy-5-*tert*-butyl-3-pyrrolyl)-*N'*-(2,3-dichlorophenyl)urea (Example 39): ^{1}H NMR (d^6-DMSO) δ 1.23 (s, 9H), 3.78 (s, 3H), 6.55 (d, J=2.9 Hz, 1H), 6.92 (t, J=7.4 Hz, 1H), 7.23 (dd, J=7.4, 8.5 Hz, 2H), 7.44 (d, J=7.7 Hz, 2H), 8.66 (s, 1H), 9.60 (s, 1H), 10.88 (br d, J=1.5 Hz, 1H); FAB-LRMS *m/z* (rel abundance) 316 (M+H, 95%).

<u>Method N-2</u>

Synthesis of *N*-(2-carbomethoxy-5-*tert*-butyl-3-pyrrolyl)-*N'*-(2,3-dichlorophenyl)urea (Example 73).

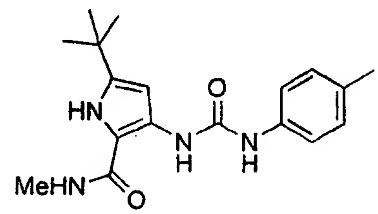


To a solution of methyl 3-amino-5-*tert*-butylpyrrole-2-carboxylate (0.99 g, 5.00 mmol) in anh. CH_2Cl_2 (50 ml) at room temp. was added a solution of 2,3-dichlorophenyl isocyanate (0.948 g, 5.00 mmol) in CH_2Cl_2 (10 mL) and the resulting mixture was allowed to stir overnight. The resulting white precipitate formed overnight was separated and washed with CH_2Cl_2 to give the desired urea (1.39 g, 67%) as a white powder: mp 200-201 °C; ^{1}H-NMR (DMSO-d_6) δ 1.23 (s, 9H), 3.78 (s, 3H), 6.50 (d, J=2.95 Hz, 1H), 7.26-7.30 (m, 2H), 7.88-7.91 (m, 1H), 9.12 (s, 1H), 9.40 (s, 1H), 10.91 (br s, 1H); FAB-

LRMS m/z 384 (M + H). Anal. Calcd for $C_{17}H_{19}N_3O_3Cl_2$: C, 53.14; H, 4.98; N, 10.94. Found: C, 53.03; H, 4.79; N, 10.86.

Method N-3

Synthesis of *N*-(2-methylcarbamoyl-5-*tert*-butyl-3-pyrrolyl)-*N'*-(4-methylphenyl)urea (Example 113).



Step 1

Methyl 5-*tert*-butyl-3-nitropyrrole-2-carboxylate was prepared as described in Method N-1 Step 3. To a solution of methyl 5-*tert*-butyl-3-nitropyrrole-2-carboxylate (10.38 g, 45.9 mmol) in a THF-MeOH-H_2O mixture(1.0:1.0:0.5, 250 mL) at room temp. was added a 1N NaOH solution (92 mL, 92 mmol) via pippette. The color of the reaction mixture turned from green to red. The mixture was warmed to the reflux temperature, maintained for 3 hr, cooled to room temp. and concentrated in vacuo. The residue was made acidic using a 10% citric acid solution and was extracted with EtOAc (2 x 50 mL). The organic layer was washed with a saturated NaCl solution, dried ($MgSO_4$), and concentrated in vacuo. The residue was triturated with hexanes to give 5-*tert*-butyl-3-nitropyrrole-2-carboxylic acid (9.70 g, 99%) as a green powder: ^1H NMR (DMSO-d_6) δ 1.24 (s, 9H), 6.41 (d, J=2.9 Hz, 1H), 12.19 (br s, 1H), 13.50 (br s, 1H).

Step 2

To a solution of 5-*tert*-butyl-3-nitropyrrole-2-carboxylic acid (2.01 g, 9.5 mmol) in a solution of anh. THF and anh. DMF (3:1, 100 mL) at 0 °C was added *N*-methylmorpholine (2.1 mL, 19 mmol, 2.0 equiv), followed by methylamine (2M in THF, 5.93 mL, 11.1 mmol, 1.25 equiv) and EDCI·HCl (2.85 g, 14.9 mmol, 1.57 equiv). The resulting mixture was allowed to warm to room temp. and stirred at that temp. overnight. The reaction mixture was diluted with H_2O (100 mL), then made acidic with a 10% citric acid solution, and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with a saturated NaCl solution, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash chromatography (15% CH_2Cl_2/hex) to give 2-(*N*-

methylcarbamoyl)-5-*tert*-butyl-3-nitropyrrole (1.40 g, 66%) as a yellow solid: ^{1}H NMR (DMSO-d_6) δ 1.29 (s, 9H), 2.76 (d, *J*=4.4 Hz, 3H), 6.36 (d, *J*=2.9 Hz, 1H), 8.59-8.60 (m, 1H), 12.19 (br s, 1H).

Step 3

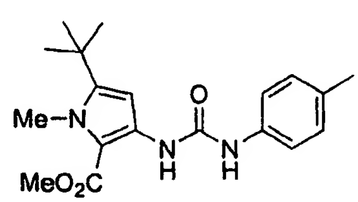
To a solution of 2-(*N*-methylcarbamoyl)-5-*tert*-butyl-3-nitropyrrole (1.0 g, 0.4 mmol) in EtOAc (50 mL) under an Ar atmosphere was added 10% Pd/C (50 mg). The mixture was evacuated then placed under a static H_2 atmosphere (1 atm.) for 24 h. The resulting slurry was filtered through a pad of Celite® with the aid of EtOAc, and the filtrate was concentrated under reduced pressure to afford 2-(*N*-methylcarbamoyl)-3-amino-5-*tert*-butylpyrrole (0.61 g, 70%): ^{1}H-NMR (DMSO-d_6) δ 1.16 (s, 9H), 2.66 (d, *J*=4.41 Hz, 3H), 4.89 (br s, 2H), 5.27 (d, *J*=2.58 Hz, 1H), 7.14-7.16 (m, 1H), 9.52 (br s, 1H).

Step 4

To a solution of 2-(*N*-methylcarbamoyl)-3-amino-5-*tert*-butylpyrrole (0.14 g, 0.70 mmol) in CH_2Cl_2 (5 mL) at room temp. was annd *p*-tolyl isocyanate (0.088 mL, 0.70 mmol, 1.0 equiv) and the resulting mixture was allowed to stir at room temp.overnight. The resulting precipitate was separated and washed with CH_2Cl_2 to give *N*-(2-methylcarbamoyl-5-*tert*-butyl-3-pyrrolyl)-*N'*-(4-methylphenyl)urea (0.17 g, 74%): mp 164-166 °C; ^{1}H-NMR (DMSO-d_6) δ 1.23 (s, 9H), 2.19 (s, 3H), 2.75 (d, *J*=4.41 Hz, 3H), 6.49 (d, *J*=2.57 Hz, 1H), 7.01 (d, *J*=8.46 Hz, 2H), 7.33 (d, *J*=8.46 Hz, 2H), 7.60-7.63 (m, 1H), 9.45 (s, 1H), 9.50 (s, 1H), 10.17 (br s, 1H); FAB-LRMS *m/z* 329 (M + H).

Method O

Synthesis of *N*-(*N*-methyl-2-carbomethoxy-5-*tert*-butyl-3-pyrrolyl)-*N'*-(4-methylphenyl)urea (Example 40).



Step 1

To a cold (0 - 10 °C) solution of methyl 5-*tert*-butyl-3-nitropyrrole-2-carboxylate (0.100 g, 0.44 mmol), benzyltributylammonium bromide (0.16 mg, 0.44 mmol, 1 equiv), and dimethyl sulfate (46 μL, 0.49 mmol, 1.1 equiv) in CH_2Cl_2 (1 mL) was added a 50%

NaOH solution (0.21 g, 2.65 mmol, 6 equiv). After 5 min, the cooling bath was removed and the mixture was stirred at room temp. for 4 h. The reaction mixture was diluted with CH_2Cl_2, washed with water and a 10% NH_4OAc solution (2x), dried (Na_2SO_4), and concentrated under reduced pressure to give a bright yellow oil. The oil was purified by flash chromatograpy (70% CH_2Cl_2/hexane) to give methyl 5-*tert*-butyl-1-methyl-3-nitropyrrole-2-carboxylate as a pale yellow oil which solidifies upon standing (0.061 g, 62%): ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 9H)., 3.80 (s, 3H), 3.92 (s, 3H), 6.47 (s, 1H).

Step 2

Methyl 5-*tert*-butyl-1-methyl-3-nitropyrrole-2-carboxylate was reduced in a manner similar to that described in Method N, Step 4 to give methyl 3-amino-5-*tert*-butyl-1-methylpyrrole-2-carboxylate as an oil (0.059 g, 100%, crude yield): ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 9H), 3.80 (s, 3H), 3.85 (s, 3H), 4.34 (br s, 2H), 5.48 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 29.7, 31.9, 34.7, 50.6, 95.7, 107.4, 142.3, 149.0, 162.2.

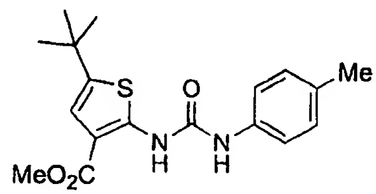
Step 3

To a solution of methyl 3-amino-5-*tert*-butyl-1-methylpyrrole-2-carboxylate (0.059 g, 0.280 mmol) and dry pyridine (1 mL) in anh. toluene (2 mL) was rapidly added phosgene (1.93M in toluene, 1.45 mL, 2.80 mmol, 10 equiv). Additional anh. toluene (3 mL) was added to aid stirring of the heterogeneous mixture. After 30 min, the orange suspension was concentrated under reduced pressure, then successively charged with anh. toluene (1 mL) and evaporated (2x). Finally, toluene (3 mL) was added followed by *p*-toluidine (0.11 mg, 1.04 mmol, 3.7 equiv). The resulting homogeneous mixture was stirred overnight, diluted with CH_2Cl_2 and washed with a 1M HCl solution. The aqueous layer was back-extracted with CH_2Cl_2 (2x). The combined organic phases were dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (10% to 25% EtOAc/ hexane) to give *N*-(*N*-methyl-2-carbomethoxy-5-*tert*-butyl-3-pyrrolyl)-*N'*-(4-methyl-2-thienyl)urea as a pale yellow solid (0.066 g, 69%): ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 9H), 2.31 (s, 3H), 3.64 (s, 3H), 3.88 (s, 3H), 6.80 (s, 1H), 7.11 (d, J = 8.4 Hz, 2H), 7.26 (app d, J = 8.4 Hz, 3H), 8.81 (br s, 1H); ^{13}C NMR ($CDCl_3$)

δ 29.8 (3C), 31.4, 32.1, 35.0, 50.4, 98.8, 108.8, 122.0 (2C), 129.5 (2C), 133.8, 134.0, 135.3, 148.6, 153.0, 162.0; FTIR (KBr) 2364 (s), 2335 (s), 1659 (m), 1579 (m), 1542 (m), 1354 (w), 1232 (w) cm^{-1}.

Method P

Synthesis of *N*-(3-carbomethoxy-5-*tert*-butyl-2-thienyl)-*N'*-(4-methylphenyl)urea (Example 44).



Step 1

To a solution of methyl cyanoacetate (4.00 g, 40.4 mmol), sulfur (1.29 g, 40.4 mmol) and DMF (20 mL) at room temp. was added Et_3N (3.04 mL, 21.8 mmol). 3,3-Dimethylbutraldehyde (5.08 g, 40.4 mmol) was added and the mixture was stirred 1 h before being poured into water (200 mL). Solids were removed by filteration and the filtrate was extracted with EtOAc. The organic layer was filtered through a plug of silica gel and concentrated under reduced pressure. The crude product was purified via flash chromatrography to afford methyl 2-amino-5-*tert*-butylthiophene-3-carboxylate (4.19 g, 49%).

Step 2

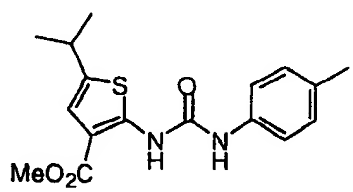
Methyl 2-amino-5-*tert*-butylthiophene-3-carboxylate was condensed with 4-methylphenyl isocyanate in a manner similar to that described in Method A, Step 2 to produce *N*-(2-carbomethoxy-5-*tert*-butyl-3-thienyl)-*N'*-(4-methylphenyl)urea (0.029 g, 18%): mp 109-111 °C; ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 9H), 2.34 (s, 3H), 3.81 (s, 3H), 6.75 (bs, 1H), 6.82 (s, 1H), 7.16 (d, *J*=8.1Hz, 2H), 7.32 (d, *J*=8.5 Hz, 2H), 10.37 (s, 1H).

Selected compound synthesized using Method P:

N-(3-Carbomethoxy-5-*tert*-butyl-2-thienyl)-*N'*-(phenyl)urea (Example 43): mp 80-2 °C; ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 9H), 3.83 (s, 3H), 6.73 (br s, 1H), 6.84 (s, 1H), 7.16 (t, *J*=7.4 Hz, 1H), 7.37 (app t, *J*=7.4 Hz, 2H), 7.52 (dd, *J*=8.1, 1.5 Hz 2H), 10.43 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 32.2 (3C), 34.2, 51.7, 109.9, 117.0, 121.3 (2C), 124.8, 129.4 (2C), 137.7, 146.0, 149.6, 151.8, 166.4; EI-LRMS *m/z* 333 (M^+).

Method Q

Synthesis of *N*-(3-carbomethoxy-5-isopropyl-2-thienyl)-*N'*-(4-methylphenyl)urea (Example 42).



Methyl 2-amino-5-isopropylthiophene-3-carboxylate was synthesized in a manner analogous to that described in Method P, Step 1.

To a solution of methyl 2-amino-5-isopropyllthiophene-3-carboxylate (0.20 g, 1.00 mmol) in anh.CH_2Cl_2 (10 mL) was added phosgene (1.93M in toluene, 2.1 mL, 4.01 mmol, 4.0 equiv) and anh. pyridine (0.32 mL, 4.01 mmol, 4.0 equiv). The $CHCl_3$ mixture was allowed to warm to room temp. and was stirred for 3 h. The resulting mixture was concentrated under reduced pressure. The residue was suspended in anh. toluene (10 mL) and *p*-toluidine (0.11 mg, 1.00 mmol, 1.0 equiv) was added. The resulting mixture was stirred overnight then separated between EtOAc (50 mL) and H_2O (50 mL). The organic phase was washed with a 1M HCl solution (2 x 25 mL), a saturated $NaHCO_3$ solution (2 x 20 mL) and a saturated NaCl solution (2 x 25 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by rotary chromatography (CH_2Cl_2), followed by preparative HPLC (SiO_2, 10% EtOAc/hexane) to give *N*-(3-carbomethoxy-5-isopropyl-2-thienyl)-*N'*-(4-methylphenyl)urea (0.15 g, 45%): mp 49-51 °C; ^{1}H NMR ($CDCl_3$) δ 1.29 (d, *J*=6.6 Hz, 6H), 2.34 (s, 3H), 3.02 (sept d, *J*=6.4, 1.1 Hz, 1H), 3.80 (s,

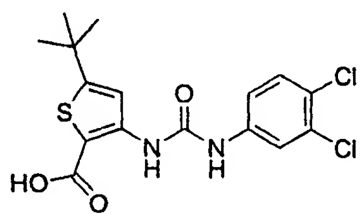
3H), 6.81 (s, 1H), 6.96 (br s, 1H), 7.17 (d, *J*=8.5 Hz, 2H), 7.32 (d, *J*=8.5 Hz, 2H), 10.4 (s, 1H); FAB-LRMS *m/z* 333 (M + H).

Selected compound synthesized using Method Q:

N-(3-Carbomethoxy-5-isopropyl-2-thienyl)-*N'*-(phenyl)urea (Example 41): mp 64-5 °C; ^{1}H NMR ($CDCl_3$) δ 1.29 (d, *J*=7.0 Hz, 6H), 3.02 (sept d, *J*=6.8, 1.1 Hz, 1H), 3.80 (s, 3H), 6.82 (d, *J*=1.1 Hz, 1H), 7.07 (br s, 1H), 7.16 (t, J=7.4 Hz, 1H), 7.37 (app t, J=7.9 Hz, 2H), 7.46 (dd, J=8.8, 1.5 Hz, 2H), 10.4 (s, 1H); FAB-LRMS *m/z* 319 (M + H).

Method R

Synthesis of *N*-(2-carboxy-5-*tert*-butyl-3-thienyl)-*N'*-(3,4-dichlorophenyl)urea (Example 66).



Step 1

A mixture of methyl 5-*tert*-butyl-3-aminothiophene-2-carboxylate (6.39 g, 30.0 mmol) and KOH (5.04 g, 90.0 mmol) in aqueous MeOH (1:1; 40 mL) was stirred at 80-90 °C for 6 h and the resulting clear solution was concentrated under reduced pressure. The gummy yellow residue was dissolved in H_2O (500 mL), treated with a phosgene solution (20% in toluene; 60 mL) dropwise over 2 h and stirred at room temp. overnight. The resulting yellow solids were removed by filtration, triturated with acetone (30 mL), and dried under reduced pressure to afford 7-*tert*-butyl-2H-thieno[3,2-d]oxazine-2,4(1H)-dione (4.25 g, 63%): ^{1}H-NMR ($CDCl_3$) δ 1.38 (s, 9H), 2.48 (s, 1H), 6.75 (s, 1H); FAB-MS *m/z* (rel abundance) 226 ($(M+H)^+$, 100%).

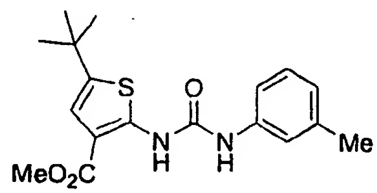
Step 2

To a solution of 7-*tert*-butyl-2H-thieno[3,2-d]oxazine-2,4(1H)-dione (0.18 g, 0.80 mmol) in THF (6 mL) was added 3,4-dichloroaniline (0.14 g, 0.86 mmol). The resulting mixture

was stirred at 70 °C for 4 h, treated with Dowex 50WX2 resin (0.060 g) and poly(4-(4-hydroxymethylphenoxy)methylstyrene) resin (0.4 g) and stirred at 70 °C for an additional 30 min. The resulting slurry was filtered, and the filtrate was concentrated under reduced pressure to give *N*-(2-carboxy-5-*tert*-butyl-3-thienyl)-*N'*-(3,4-dichlorophenyl)urea (0.061 g, 20%): HPLC ES-MS *m/z* (rel abundance) 386 ($(M+H)^+$).

Method S

Synthesis of *N*-(3-carbomethoxy-5-*tert*-butyl-2-thienyl)-*N'*-(3-methylphenyl)urea (Example 122).



Step 1

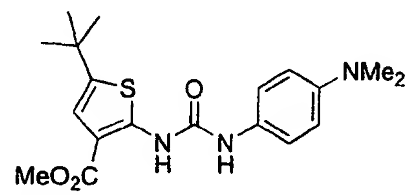
To a solution of trichloromethyl chloroformate (diphosgene; 7.0 g, 35.3 mmol) in CH_2Cl_2 (100 mL) was added methyl 2-amino-5-*tert*-butylthiophene-3-carboxylate (5.0 g, 23.5 mmol) and pyridine (2.8 g, 35.3 mmol). The reaction mixture was heated to the reflux temp. for 10 h, filtered through a pad of silica, and concentrated under reduced pressure. The residue was dissolved in toluene and the resulting solution was concentrated under reduced pressure to give 3-methoxycarbonyl-5-*tert*-butylthiophene-2-isocyanate contaminated with a side product. 3-Methoxycarbonyl-5-*tert*-butylthiophene-2-isocyanate: ^{1}H-NMR ($CDCl_3$) δ 1.34 (s, 9H), 3.88 (s, 3H), 6.95 (s, 1H). Side product: ^{1}H-NMR ($CDCl_3$) d 1.37 (s, 9H), 3.89 (s, 3H), 6.88 (s, 1H), 10.92 (br s, 1H). This material was used in the next step without further purification.

Step 2

A solution of 3-methoxycarbonyl-5-*tert*-butylthiophene-2-isocyanate in toluene (0.16M, 2.5 mL 0.4 mmol) was added to 3-methylaniline (0.053 g, 0.5 mmol). The resulting mixture was stirred at 60 °C for 4 h, cooled to room temp., then treated with a 2M H_2SO_4 solution (0.7 mL). EtOAc (4 mL) was added and the mixture was stirred vigorously. The mixture was passed through a filtration cartridge (0.8 g Extrelute® and 3 g silica gel) with the aid of EtOAc (8 mL), then concentrated under reduced pressure (speedvac: 2 h at 43 °C; 1 h at 60°C) to afford *N*-(3-carbomethoxy-5-*tert*-butyl-2-thienyl)-*N'*-(3-methylphenyl)urea (0.11 g, 80%): ^{1}H-NMR ($CDCl_3$) δ 1.35 (s, 9H), 2.36 (s, 3H), 3.82 (s, 3H), 6.82 (s, 1H), 6.93-7.01 (m, 2H), 7.13-7.29 (m, 2H), 7.35 (br s, 1H), 10.44 (s, 1H).

Method T

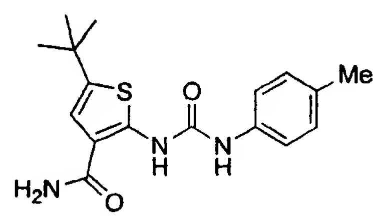
Synthesis of *N*-(3-carbomethoxy-5-*tert*-butyl-2-thienyl)-*N'*-(4-dimethylaminophenyl)urea (Example 142).



A solution of 3-methoxycarbonyl-5-*tert*-butylthiophene-2-isocyanate in toluene (0.16M, 2.5 mL 0.4 mmol) was added to 4-(*N,N*-dimethylamino)aniline (0.054 g, 0.4 mmol). The reaction mixture was stirred at 60 °C for 4 h, then concentrated under reduced pressure (speedvac: 2 h at 43 °C; 1 h at 60 °C). The crude product was purified by flash chromatography (SiO_2, EtOAc/pet. ether) to afford *N*-(3-carbomethoxy-5-*tert*-butyl-2-thienyl)-*N'*-(4-dimethylaminophenyl)urea (0.099 g, 66%): ^{1}H-NMR ($CDCl_3$) δ 1.35 (s, 9H), 3.0 (br s, 6H), 3.75 (s, 3H), 6.6-7.0 (m, 3H), 7.1-7.5 (m, 3H), 10.25 (br s, 1H).

Method U

Synthesis of *N*-(3-carbamoyl-5-*tert*-butyl-2-thienyl)-*N'*-(4-methylphenyl)urea (Example 119).



Step 1

A mixture of α-cyanoacetamide (1.68 g, 20 mmol), sulfur (0.64 g, 20 mmol) and 3,3-dimethylbutanal (2.0 g, 20 mmol) in MeOH (20 mL) was heated to the reflux temp. and morpholine (1.74 g, 20 mmol) was added within 10 min. The reaction mixture was stirred at the reflux temp.for 8.5 h, then concentrated under reduced pressure The residue was purified by flash chromatography (50% EtOAc/50% pet. ether) to give 2-amino-5-*tert*-butylthiophene-3-carboxamide (2.94 g, 74%): ^{1}H-NMR ($CDCl_3$) δ 1.3 (s, 9H), 5.48 (br s, 4H), 6.37 (s, 1H).

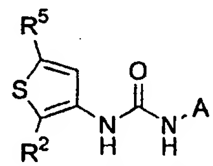
Step 2

A solution of 2-amino-5-*tert*-butylthiophene-3-carboxamide (0.14 g, 0.7 mmol) and *p*-tolyl isocyanate (0.093 g, 0.7 mmol) in toluene (5 mL) was stirred at 60 °C overnight.

The reaction mixture was separated between with water (10 mL) and EtOAc (10 mL). The aqueous phase was back-extracted with EtOAc (3 x 10 mL), and the combined organic phases were washed with a saturated NaCl solution (25 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by chromatography (SiO_2; gradient from 20% EtOAc/80% pet. ether to 30% EtOAc/70% pet ether) to give *N*-(3-carbamoyl-5-*tert*-butyl-2-thienyl)-*N'*-(4-methylphenyl)urea (0.092 g, 40 %): ^{1}H-NMR ($CDCl_3$) δ 1.38 (s, 9H), 2.32 (s, 3H), 5.58 (br s, 2H), 6.53 (s, 1H), 7.13 (app d, 2H), 7.35 (app d, 2H), 7.45 (br, 1H), 11.23 (br s, 1H).

The following compounds have been synthesized according to the general methods listed above:

Table 1 3-Urido Thiophenes



#	R^2	R^5	A	mp (°C)	TLC (R_f)	TLC Conditions	MS	MS Source	Method
1	CO_2Me	iPr	C_6H_5	108-10					A
2	CO_2Me	*tert*-Bu	C_6H_5	106-8					A
3	CO_2iPr	*tert*-Bu	C_6H_5	65-7					D
4	CO_2H	*tert*-Bu	4-MeC_6H_4				333 (M+H)	FAB	H
5	CO_2Me	*tert*-Bu	4-MeC_6H_4	124-6					A
6	CO_2Et	*tert*-Bu	4-MeC_6H_4				360 (M^+)	EI	D
53	CO_2Pr-*n*	*tert*-Bu	4-MeC_6H_4	59-66	0.38	10% EtOAc / 90% hex	375 (M+H)	FAB	E
7	CO_2iPr	*tert*-Bu	4-MeC_6H_4	72-86	0.34	10% EtOAc / 90% hex	375 (M+H)	FAB	E
8	CO_2All	*tert*-Bu	4-MeC_6H_4	52-62	0.34	10% EtOAc / 90% hex	373 (M+H)	FAB	E
9	CO_2Me	*tert*-Bu	3-MeC_6H_4	70-2			347 (M+H)	FAB	B

Table 1 3-Urido Thiophenes - continued

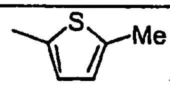
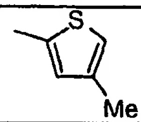
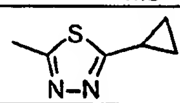
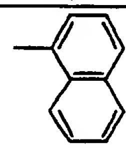
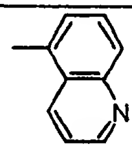
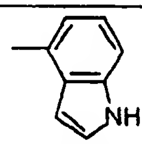
#	R^2	R^5	A	mp (°C)	TLC (R_f)	TLC Conditions	MS	MS Source	Method
54	CO_2Me	*tert*-Bu	4-FC_6H_4	160-2	0.45	20% EtOAc / 80% hex	351 (M+H)	FAB	B
10	CO_2Me	*tert*-Bu	2-HOC_6H_4	75-7					B
11	CO_2Me	*tert*-Bu	2-$H_2NC_6H_4$				348 (M+H)	FAB	C
13	CO_2Me	*tert*-Bu	3,4-$Me_2C_6H_3$	68-71					A
14	CO_2Me	*tert*-Bu		118-20			353 (M+H)	FAB	J
15	CO_2Me	*tert*-Bu					353 (M+H)	FAB	J
16	CO_2Me	*tert*-Bu		188-9			381 (M+H)	FAB	B
17	CO_2Me	*tert*-Bu		109-11					A
18	CO_2Me	*tert*-Bu		181-2					B
19	CO_2Me	*tert*-Bu		92-3					B
55	CO_2Me	*tert*-Bu	4-ClC_6H_4	150-2					B
56	CO_2Me	*tert*-Bu	4-HOC_6H_4	198-9					B
57	CO_2Me	*tert*-Bu	4-$H_2NC_6H_4$		0.06	20% EtOAc / 80% hex			C
58	CO_2Me	*tert*-Bu	4-EtC_6H_4				361 (M+H)	FAB	B

Table 1 3-Urido Thiophenes - continued

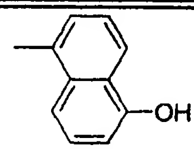
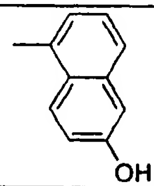
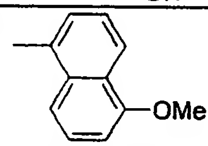
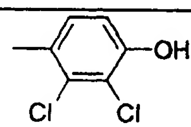
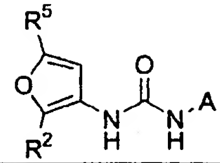
#	R^2	R^5	A	mp (°C)	TLC (R_f)	TLC Conditions	MS	MS Source	Method
67	CO_2Me	*tert*-Bu		131-5	0.30	30% EtOAc / 70% hex	399 (M+H)	FAB	B
68	CO_2Me	*tert*-Bu		112	0.41	35% EtOAc / 65% hex	399 (M+H)	FAB	B
69	CO_2Me	*tert*-Bu		110	0.37	25% EtOAc / 65% hex	399 (M+H)	FAB	B
70	CO_2Me	*tert*-Bu	$3\text{-}MeO_2CC_6H_4$		0.24	20% Et_2O / 80% pet ether	405 (M+H)	EI	B
71	CO_2Me	*tert*-Bu	$2,3\text{-}Cl_2C_6H_3$		0.44	20% Et_2O / 80% pet ether	401 (M+H)	CI	B
76	CO_2Me	*tert*-Bu			0.11	20% Et_2O / 80% pet ether	417 (M+H)	EI	B
22	C(O)NHMe	*tert*-Bu	$4\text{-}MeC_6H_4$	202-4					F or G
23	C(O)NHMe	*tert*-Bu	$4\text{-}EtC_6H_4$	101-4	0.18	20% EtOAc / 80% hex	360 (M+H)	FAB	G
24	C(O)NHMe	*tert*-Bu	$4\text{-}iPrC_6H_4$	113-20	0.20	20% EtOAc / 80% hex	374 (M+H)	FAB	G
25	C(O)NHMe	*tert*-Bu	$4\text{-}FC_6H_4$	203-4	0.61	5% MeOH / 95% CH_2Cl_2	349 (M^+)	EI	F or G
26	C(O)NHMe	*tert*-Bu	$3,4\text{-}Me_2C_6H_3$	180-2					G
27	C(O)NHMe	*tert*-Bu	$2,4\text{-}Me_2C_6H_3$	195-6			359 (M^+)	EI	G
28	C(O)NHMe	*tert*-Bu	$3\text{-}Cl\text{-}4\text{-}MeC_6H_3$	178-9			379 (M^+)	EI	G

Table 1 3-Urido Thiophenes - continued

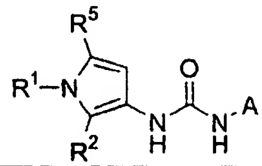
#	R^2	R^5	A	mp (°C)	TLC (R_f)	TLC Conditions	MS	MS Source	Method
29	C(O)NHMe	*tert*-Bu	3-F-4-MeC_6H_3	182-3			364 (M+H)	FAB	G
30	C(O)NHMe	*tert*-Bu	3-Cl-4-FC_6H_3	203-4			386 (M+H)	FAB	G
31	C(O)NHMe	*tert*-Bu	2,4-$F_2C_6H_3$	213-5					G
59	C(O)NHMe	*tert*-Bu	3,4-$F_2C_6H_3$				368 (M+H)	FAB	G
60	C(O)NHMe	*tert*-Bu	2-F-4-MeC_6H_3				364 (M+H)	FAB	G
61	C(O)NHMe	*tert*-Bu	2-Cl-4-MeC_6H_3				380 (M+H)	FAB	G
62	C(O)NHMe	*tert*-Bu	2,3,4-$Me_3C_6H_2$		0.88	50% EtOAc / 50% hex	374 (M+H)	FAB	G
63	C(O)NHMe	*tert*-Bu	3-Me-4-FC_6H_3				364 (M+H)	FAB	G
64	C(O)NHMe	*tert*-Bu	2-Cl-4-FC_6H_3				384 (M+H)	FAB	G
65	C(O)NHMe	*tert*-Bu	2-Me-4-FC_6H_3				364 (M+H)	FAB	G
66	CO_2H	*tert*-Bu	3,4-$Cl_2C_6H_3$				387 (M+H)	HPLC ES-MS	R

Table 2 3-Urido Furans



#	R^2	R^5	A	mp (°C)	TLC (R_f)	TLC Conditions	MS	MS Source	Method
32	CO_2Me	*tert*-Bu	4-MeC_6H_4	78-9	0.46	20% EtOAc / 80% hex	331 (M+H)	FAB	K, L-1 or L-2
33	CO_2Me	*tert*-Bu	4-FC_6H_4	81-2	0.37	20% EtOAc / 80% hex	335 (M+H)	FAB	L-1 or L-2
34	CO_2Me	*tert*-Bu	2,3-$Cl_2C_6H_4$	195-7	0.58	20% EtOAc / 80% hex	385 (M+H)	HPLC ES-MS	L-1 or L-2
72	CO_2Me	*tert*-Bu	3,4 -$Cl_2C_6H_4$	83-8 (dec)	0.19	10% EtOAc / 90% hex	385 (M+H)	FAB	L-1 or L-2
35	C(O)NHMe	*tert*-Bu	4-MeC_6H_4	190-3	0.25	20% EtOAc / 80% hex	330 (M+H)	FAB	M
36	C(O)NHMe	*tert*-Bu	4-FC_6H_4	109-11	0.21	20% EtOAc / 80% hex	334 (M+H)	FAB	M

Table 3 3-Urido Pyrroles



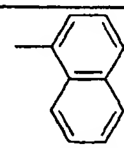
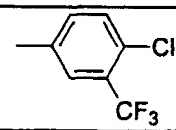
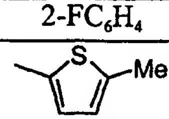
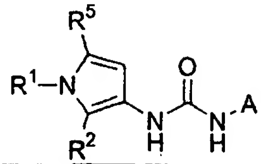
#	R^1	R^2	R^5	A	mp (°C)	MS	MS Source	Method
37	H	CO_2Me	*tert*-Bu	C_6H_5	262-3 (dec)	316 (M+H)	FAB	N-1 or N-2
38	H	CO_2Me	*tert*-Bu	$4\text{-}MeC_6H_4$	257-8	330 (M+H)	FAB	N-1 or N-2
39	H	CO_2Me	*tert*-Bu	$3,4\text{-}Cl_2C_6H_3$	177-8	384 (M+H)	FAB	N-1 or N-2
73	H	CO_2Me	*tert*-Bu	$2,3\text{-}Cl_2C_6H_3$	194-6	384 (M+H)	FAB	N-2
74	H	CO_2Me	*tert*-Bu		195-6	366 (M+H)	FAB	N-2
75	H	CO_2Me	*tert*-Bu	$4\text{-}FC_6H_4$	214-46			N-2
76	H	CO_2Me	*tert*-Bu		169-70	418 (M+H)	FAB	N-2
78	H	CO_2Me	*tert*-Bu	$2,4\text{-}F_2C_6H_3$	233-4	352 (M+H)	FAB	N-2
79	H	CO_2Me	*tert*-Bu	$3\text{-}FC_6H_4$	245-6 (dec)	333 (M^+)	EI	N-2
80	H	CO_2Me	*tert*-Bu	$2\text{-}ClC_6H_4$	252-3	350 (M+H)	FAB	N-2
81	H	CO_2Me	*tert*-Bu	$3,5\text{-}Cl_2C_6H_3$	169-70	384 (M+H)	FAB	N-2
82	H	CO_2Me	*tert*-Bu	$3\text{-}ClC_6H_4$	177-8	350 (M+H)	FAB	N-2
83	H	CO_2Me	*tert*-Bu	$2\text{-}FC_6H_4$	242-3			N-2
84	H	CO_2Me	*tert*-Bu		233-4	336 (M+H)	FAB	N-2
85	H	CO_2Me	*tert*-Bu	$3,5\text{-}Me_2C_6H_3$	228-9	344 (M+H)	FAB	N-2

Table 3 3-Urido Pyrroles - continued



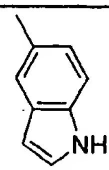
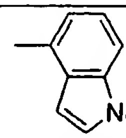
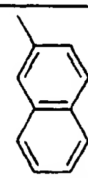
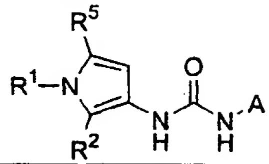
#	R^1	R^2	R^5	A	mp (°C)	MS	MS Source	Method
86	H	CO_2Me	*tert*-Bu	2-MeC_6H_4	191-2	330 (M+H)	FAB	N-2
87	H	CO_2Me	*tert*-Bu		242-3	355 (M+H)	FAB	N-2
88	H	CO_2Me	*tert*-Bu		245-6	355 (M+H)	FAB	N-2
89	H	CO_2Me	*tert*-Bu	3-MeC_6H_4	191-2	330 (M+H)	FAB	N-2
90	H	CO_2Me	*tert*-Bu		210-1	366 (M+H)	FAB	N-2
91	H	CO_2Me	*tert*-Bu	3-Cl-4-FC_6H_3	193-4	368 (M+H)	FAB	N-2
92	H	CO_2Me	*tert*-Bu	3-Cl-4-MeC_6H_3	185-6	364 (M+H)	FAB	N-2
93	H	CO_2Me	*tert*-Bu	2-Me-4-ClC_6H_3	226-7	364 (M+H)	FAB	N-2
94	H	CO_2Me	*tert*-Bu	2-Me-5-ClC_6H_3	196-7			N-2
95	H	CO_2Me	*tert*-Bu	2,4-$Me_2C_6H_3$	258-9			N-2
96	H	CO_2Me	*tert*-Bu	3,4-$Me_2C_6H_3$	195-6			N-2
97	H	CO_2Me	*tert*-Bu	2,5-$F_2C_6H_3$	228-30			N-2
98	H	CO_2Me	*tert*-Bu	4-$Me_2NC_6H_4$	235-7	358 (M^+)	EI	N-2
99	H	CO_2Me	*tert*-Bu	4-$H_2NC_6H_4$	242-4	331 (M+H)	FAB	N-2

Table 3 3-Urido Pyrroles - continued



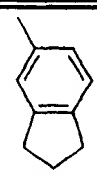
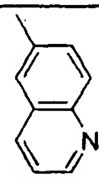
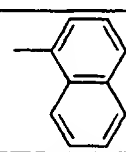
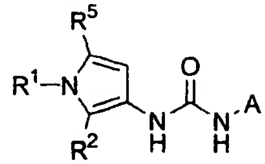
#	R^1	R^2	R^5	A	mp (°C)	MS	MS Source	Method
100	H	CO_2Me	*tert*-Bu		192-4	355 (M^+)	EI	N-2
105	H	CO_2Me	*tert*-Bu		230-1	367 (M+H)	FAB	N-2
106	H	CO_2Me	*tert*-Bu	2-BrC_6H_4	253-4	394 (M+H)	FAB	N-2
107	H	CO_2Me	*tert*-Bu	4-BrC_6H_4	248-9	394 (M+H)	FAB	N-2
108	H	CO_2Me	*tert*-Bu	2,4-$Cl_2C_6H_3$	200-1	383 (M^+)	EI	N-2
109	H	CO_2Me	*tert*-Bu	4-*tert*-BuC_6H_4	188-91	372 (M+H)	FAB	N-2
110	H	CO_2Me	*tert*-Bu	4-$iPrOC_6H_4$	139-40	374 (M+H)	FAB	N-2
111	H	CO_2Me	*tert*-Bu	4-ClC_6H_4	257-8 (dec)	350 (M+H)	FAB	N-2
112	H	CO_2Me	*tert*-Bu	3-$F_3CC_6H_4$	138-9	384 (M+H)	FAB	N-2
113	H	C(O)NHMe	*tert*-Bu	4-MeC_6H_4	164-6	329 (M+H)	FAB	N-3
114	H	C(O)NHMe	*tert*-Bu	2,3-$Cl_2C_6H_3$	227-8	383 (M+H)	FAB	N-3
115	H	C(O)NHMe	*tert*-Bu		177-8	365 (M+H)	FAB	N-3
40	Me	CO_2Me	*tert*-Bu	4-MeC_6H_4	171-2	343 (M^+)	EI	O

Table 3 3-Urido Pyrroles - continued



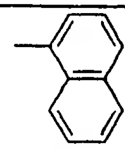
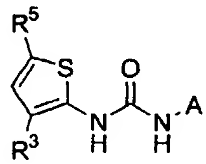
#	R^1	R^2	R^5	A	mp (°C)	MS	MS Source	Method
101	Me	CO_2Me	*tert*-Bu	2,3-$Cl_2C_6H_4$	94-7	398 (M+H)	FAB	O
102	Me	CO_2Me	*tert*-Bu		178-9	380 (M+H)	FAB	O
103	Me	CO_2Me	*tert*-Bu	C_6H_5	175-6	330 (M+H)	FAB	O
104	Me	CO_2Me	*tert*-Bu	4-FC_6H_4	211-2	347 (M^+)	EI	O

Table 4 2-Urido Thiophenes



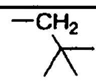
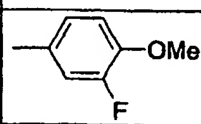
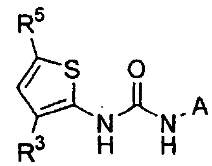
#	R^3	R^5	A	mp (°C)	TLC (R_f)	TLC Conditions	MS	MS Source	Method
41	CO_2Me	iPr	C_6H_5	64-5			319 (M+H)	FAB	Q
42	CO_2Me	iPr	4-MeC_6H_4	49-51			333 (M^+)	EI	Q
43	CO_2Me	*tert*-Bu	C_6H_5	80-2			333 (M^+)	EI	P
44	CO_2Me	*tert*-Bu	4-MeC_6H_4	109-11					P
116	CO_2Me		4-MeC_6H_4	141-2					Q
117	CO_2Me	*tert*-Bu			0.20	20% Et_2O / 80% pet ether	381 (M+H)	EI	S
118	CO_2Me	*tert*-Bu	2,3-$Cl_2C_6H_3$		0.45	20% Et_2O / 80% pet ether	401 (M+H)	CI	S

Table 4 2-Urido Thiophenes - continued



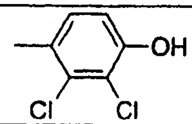
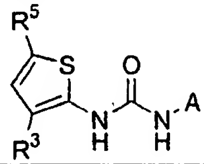
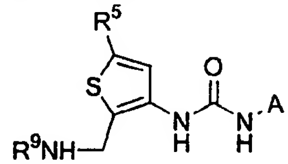
#	R^3	R^5	A	mp (°C)	TLC (R_f)	TLC Conditions	MS	MS Source	Method
119	$C(O)NH_2$	*tert*-Bu	4-MeC_6H_4		0.19	50% Et_2O / 50% pet ether	332 (M+H)	CI	U
120	CO_2Me	*tert*-Bu			0.13	20% Et_2O / 80% pet ether	417 (M+H)	EI	S
121	CO_2Me	*tert*-Bu	2-MeC_6H_4		0.32	20% Et_2O / 80% pet ether	347 (M+H)	HPLC ES-MS	S
122	CO_2Me	*tert*-Bu	3-MeC_6H_4		0.34	20% Et_2O / 80% pet ether	347 (M+H)	HPLC ES-MS	S
123	CO_2Me	*tert*-Bu	4-$iPrC_6H_4$		0.38	20% Et_2O / 80% pet ether	375 (M+H)	HPLC ES-MS	S
124	CO_2Me	*tert*-Bu	3-$MeOC_6H_4$		0.24	20% Et_2O / 80% pet ether	363 (M+H)	HPLC ES-MS	S
125	CO_2Me	*tert*-Bu	4-$MeOC_6H_4$		0.18	20% Et_2O / 80% pet ether	363 (M+H)	HPLC ES-MS	S
126	CO_2Me	*tert*-Bu	4-*n*-$BuOC_6H_4$		0.32	20% Et_2O / 80% pet ether	405 (M+H)	HPLC ES-MS	S
127	CO_2Me	*tert*-Bu	2-HOC_6H_4		0.49	50% Et_2O / 50% pet ether	349 (M+H)	HPLC ES-MS	S
128	CO_2Me	*tert*-Bu	3-HOC_6H_4		0.43	50% Et_2O / 50% pet ether	349 (M+H)	HPLC ES-MS	S
129	CO_2Me	*tert*-Bu	4-HOC_6H_4		0.38	50% Et_2O / 50% pet ether	349 (M+H)	HPLC ES-MS	S
130	CO_2Me	*tert*-Bu	2,4-$Me_2C_6H_3$		0.34	20% Et_2O / 80% pet ether	361 (M+H)	HPLC ES-MS	S
131	CO_2Me	*tert*-Bu	2,5-$Me_2C_6H_3$		0.36	20% Et_2O / 80% pet ether	361 (M+H)	HPLC ES-MS	S

Table 4 2-Urido Thiophenes - continued



#	R^3	R^5	A	mp (°C)	TLC (R_f)	TLC Conditions	MS	MS Source	Method
132	CO_2Me	*tert*-Bu	3,4-$Me_2C_6H_3$		0.34	20% Et_2O / 80% pet ether	361 (M+H)	HPLC ES-MS	S
133	CO_2Me	*tert*-Bu	3,5-$Me_2C_6H_3$		0.36	20% Et_2O / 80% pet ether	361 (M+H)	HPLC ES-MS	S
134	CO_2Me	*tert*-Bu	2,3-$F_2C_6H_3$		0.44	20% Et_2O / 80% pet ether	369 (M+H)	HPLC ES-MS	S
135	CO_2Me	*tert*-Bu	2,6-$F_2C_6H_3$		0.25	20% Et_2O / 80% pet ether	369 (M+H)	HPLC ES-MS	S
136	CO_2Me	*tert*-Bu	2-FC_6H_4		0.42	20% Et_2O / 80% pet ether	351 (M+H)	HPLC ES-MS	S
137	CO_2Me	*tert*-Bu	3-FC_6H_4		0.31	20% Et_2O / 80% pet ether	351 (M+H)	HPLC ES-MS	S
138	CO_2Me	*tert*-Bu	4-FC_6H_4		0.31	20% Et_2O / 80% pet ether	351 (M+H)	HPLC ES-MS	S
139	CO_2Me	*tert*-Bu	2-ClC_6H_4		0.41	20% Et_2O / 80% pet ether	367 (M+H)	HPLC ES-MS	S
140	CO_2Me	*tert*-Bu	3-ClC_6H_4		0.31	20% Et_2O / 80% pet ether	367 (M+H)	HPLC ES-MS	S
141	CO_2Me	*tert*-Bu	2,4-$F_2C_6H_3$		0.40	20% Et_2O / 80% pet ether	369 (M+H)	HPLC ES-MS	S
142	CO_2Me	*tert*-Bu	4-$Me_2NC_6H_3$		0.45	50% Et_2O / 50% pet ether	376 (M+H)	EI	T
143	CO_2Me	*tert*-Bu	2,5-$F_2C_6H_3$		0.39	20% Et_2O / 80% pet ether	369 (M+H)	HPLC ES-MS	S
144	$C(O)NH_2$	*tert*-Bu	2,3-$Cl_2C_6H_3$		0.46	40% Et_2O / 60% pet ether	386 (M^+)	EI	U

Table 5 2-Aminomethyl-3-urido Thiophenes



#	R^5	R^9	A	mp (°C)	MS	MS Source	Method
50	*tert*-Bu	$C(O)CH_3$	$4\text{-}MeC_6H_4$	203-5	360 (M+H)	FAB	I
51	*tert*-Bu	$C(O)CH_2NH_2$	$4\text{-}MeC_6H_4$	93-6			I
52	*tert*-Bu	$C(O)CH_2NHBOC$	$4\text{-}MeC_6H_4$	174-6			I

BIOLOGICAL EXAMPLES

P38 Kinase Assay:

The *in vitro* inhibitory properties of compounds were determined using a p38 kinase inhibition assay. P38 activity was detected using an *in vitro* kinase assay run in 96-well microtiter plates. Recombinant human p38 (0.5 μg/mL) was mixed with substrate (myelin basic protein, 5 μg/mL) in kinase buffer (25 mM Hepes, 20 mM $MgCl_2$ and 150 mM NaCl) and compound. One μCi/well of ^{33}P-labeled ATP (10 μM) was added to a final volume of 100 μL. The reaction was run at 32 °C for 30 min. and stopped with a 1M HCl solution. The amount of radioactivity incorporated into the substrate was determined by trapping the labeled substrate onto negatively charged glass fiber filter paper using a 1% phosphoric acid solution and read with a scintillation counter. Negative controls included substrate plus ATP alone.

All compounds exemplified displayed p38 IC_{50}s of between 1 nM and 10 μM.

LPS Induced TNFα Production in Mice:

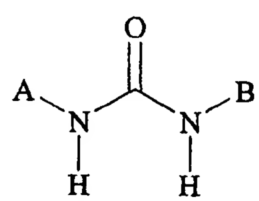
The *in vivo* inhibitory properties of selected compounds were determined using a murine LPS induced TNFα production *in vivo* model. BALB/c mice (Charles River Breeding Laboratories; Kingston, NY) in groups of ten were treated with either vehicle or compound by the route noted. After one hour, endotoxin (E. coli lipopolysaccharide (LPS) 100 μg) was administered intraperitoneally (i.p.). After 90 min, animals were

euthanized by carbon dioxide asphyxiation and plasma was obtained from individual animals by cardiac puncture ionto heparinized tubes. The samples were clarified by centrifugation at 12,500 x *g* for 5 min at 4 °C. The supernatants were decanted to new tubes, which were stored as needed at -20 °C. TNFα levels in sera were measured using a commercial murine TNF ELISA kit (Genzyme).

The preceeding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceeding examples

WHAT IS CLAIMED IS:

1. A method for the treatment of a disease, other than cancer, mediated by p38, comprising administering a compound of Formula I

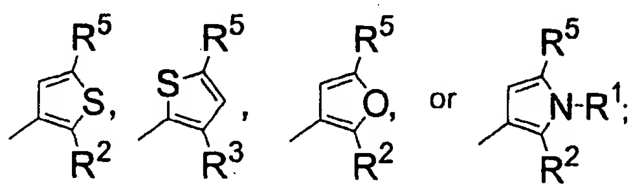


I

wherein

A is optionally substituted C_{6-12}-aryl or C_{5-12}-heteroaryl;

B is



R^1 is H or C_{1-4}-alkyl;

R^2 and R^3 are each independently halogen, -COOR^1, -CN, -CONR^{7}R^8, or -CH$_2$NHR^9;

R^5 is C_{3-5}-alkyl;

R^6 is C_{1-6}-alkyl;

R^7 is hydrogen;

R^8 is methyl;

R^9 is hydrogen, methyl or -CO-R^{10}; and

R^{10} is hydrogen or methyl optionally substituted by NR$^6_2$ or COOR^6.

2. A method according to claim 1, wherein the disease is mediated by a cytokine or protease regulated by p38.

3. A method according to claim 1, wherein A is C_{6-12}-aryl or C_{5-12}-heteroaryl optionally substituted by C_{1-4}-alkyl, C_{3-6}-cycloalkyl, halogen, -OH, -OR^1, or -$NR^1{}_2$.

4. A method according to claim 1, wherein R^5 is isopropyl or *tert*-butyl.

5. A method according to claim 1, wherein A is phenyl, 1,3,4-thiadiazol-2- or -5-yl, 7-indolyl, or 8-quinolinyl, each optionally substituted by C_{1-4}-alkyl, C_{3-6}-cycloalkyl, halogen, -OH, -OR^1, or -$N^1{}_2$.

6. A method according to claim 1, wherein A is 4-methylphenyl, 4-fluorophenyl, 5-methyl-2-thienyl, 4-methyl-2-thienyl, or 5-cyclopropyl-1,3,4-thiadiazol-2-yl.

7. A method according to claim 1, wherein R^2 or R^3 is -$COOR^1$ or CH_2NHR^9, and R^1 is C_{1-4}-alkyl, R^7 is H, and R^8 is C_{1-10}-alkyl.

8. A method according to claim 1, comprising administering an amount of a compound of Formula I effective to inhibit p38.

9. A method according to claim 2, wherein the disease is mediated by TNFα, MMP-1, MMP-3, IL-1, IL-6, or IL-8.

10. A method according to claim 1, wherein the disease is an inflammatory or immunomodulatory disease.

11. A method according to claim 1, wherein the disease is rheumatoid arthritis, osteoperosis, asthma, septic shock, inflammatory bowel disease, or the result of host-versus-graft reactions.

12. A method according to claim 1, wherein the compound is *N*-(2-carbomethoxy-5-isopropyl-3-thienyl)-*N'*-(phenyl)urea; *N*-(2-carbomethoxy-5-*tert*-butyl-3-thienyl)-*N'*-(4-methylphenyl)urea; *N*-(2-carbomethoxy-5-*tert*-butyl-3-thienyl)-*N'*-(4-fluorophenyl)urea; *N*-(2-carbomethoxy-5-*tert*-butyl-3-thienyl)-*N'*-(3-methylphenyl)urea; *N*-(2-carbomethoxy-5-*tert*-butyl-3-thienyl)-*N'*-(5-cyclopropyl-2-thiadiazolyl)urea; *N*-(2-carbomethoxy-5-*tert*-butyl-3-thienyl)-*N'*-(2-aminophenyl)urea; *N*-(2-carboethoxy-5-*tert*-butyl-3-thienyl)-*N'*-(4-methylphenyl)urea; *N*-(2-(carbo-1-prop-2-enyloxy)-5-*tert*-butyl-3-thienyl)-*N'*-(4-methylphenyl)urea; *N*-(2-(carbo-2-propyloxy)-5-*tert*-butyl-3-thienyl)-*N'*-(4-methylphenyl)urea; *N*-(2-(carbo-1-propyloxy)-5-*tert*-butyl-3-thienyl)-*N'*-(4-methylphenyl)urea; *N*-(2-methylcarbamoyl-5-*tert*-butyl-3-thienyl)-*N'*-(4-methylphenyl)urea; *N*-(2-methylcarbamoyl-5-*tert*-butyl-3-thienyl)-*N'*-(4-fluorophenyl)urea; *N*-(2-methylcarbamoyl)-5-*tert*-butyl-3-thienyl)-*N'*-(4-ethylphenyl)urea; *N*-(2-methylcarbamoyl)-5-*tert*-butyl-3-thienyl)-*N'*-(4-isopropylphenyl)urea; *N*-(2-methylcarbamoyl)-5-*tert*-butyl-3-thienyl)-*N'*-(2,4-dimethylphenyl)urea; *N*-(2-methylcarbamoyl)-5-*tert*-butyl-3-thienyl)-*N'*-(3-chloro-4-methylphenyl)urea; *N*-(2-methylcarbamoyl)-5-*tert*-butyl-3-thienyl)-*N'*-(3-fluoro-4-methylphenyl)urea; *N*-(2-methylcarbamoyl)-5-*tert*-butyl-3-thienyl)-*N'*-(3-chloro-4-fluorophenyl)urea; *N*-(2-carboxy-5-*tert*-butyl-3-thienyl)-*N'*-(4-methylphenyl)urea; *N*-(2-(*N*-glycylaminomethyl)-5-*tert*-butyl-3-thienyl)-*N'*-(4-methylphenyl)urea; *N*-(2-(*N*-(*N*-carbo-*tert*-butoxyglycyl)aminomethyl)-5-*tert*-butyl-3-thienyl)-*N'*-(4-methylphenyl)urea; *N*-(2-(*N*-acetylaminomethyl)-5-*tert*-butyl-3-thienyl)-*N'*-(4-methylphenyl)urea; *N*-(2-carbomethoxy-5-*tert*-butyl-3-thienyl)-*N'*-(4-methyl-2-thienyl)urea; or *N*-(2-carbomethoxy-5-*tert*-butyl-3-thienyl)-*N'*-(5-methyl-2-thienyl)urea.

13. A method according to claim 1, wherein the compound is *N*-(2-carbomethoxy-5-*tert*-butyl-3-furyl)-*N'*-(4-methylphenyl)urea; *N*-(2-carbomethoxy-5-*tert*-butyl-3-furyl)-*N'*-(4-fluorophenyl)urea; *N*-(2-carbomethoxy-5-*tert*-butyl-3-furyl)-*N'*-(2,3-dichlorophenyl)urea; *N*-(2-methylcarbamoyl-5-*tert*-butyl-3-furyl)-*N'*-(4-fluorophenyl)urea; or *N*-(2-methylcarbamoyl-5-~~*tert*-bu~~tylfuryl)-*N'*-(4-methylphenyl)urea.

14. A method according to claim 1, wherein the compound is *N*-(2-carbomethoxy-5-*tert*-butyl-3-pyrrolyl)-*N'*-(4-methylphenyl)urea; *N*-(2-carbomethoxy-5-*tert*-butyl-3-pyrrolyl)-*N'*-(phenyl)urea; *N*-(2-carbomethoxy-5-*tert*-butyl-3-pyrrolyl)-*N'*-(2,3-dichlorophenyl)urea; or *N*-(*N*-methyl-2-carbomethoxy-5-*tert*-butyl-3-pyrrolyl)-*N'*-(5-methyl-2-thienyl)urea.

15. A method according to claim 1, wherein the compound is *N*-(3-carbomethoxy-5-*tert*-butyl-2-thienyl)-*N'*-(4-methylphenyl)urea; *N*-(3-carbomethoxy-5-*tert*-butyl-2-thienyl)-*N'*-(phenyl)urea; *N*-(3-carbomethoxy-5-isopropyl-2-thienyl)-*N'*-(4-methylphenyl)urea; or *N*-(3-carbomethoxy-5-isopropyl-2-thienyl)-*N'*-(phenyl)urea.

16. A method according to claim 1, wherein the compound is *N*-(2-methylcarbamoyl-5-*tert*-butyl-3-furyl)-*N'*-(3,4-dichlorophenyl)urea; *N*-(2-carbomethoxy-5-*tert*-butyl-3-pyrrolyl)-*N'*-(2,3-dichlorophenyl)urea; *N*-(2-carbomethoxy-5-*tert*-butyl-3-pyrrolyl)-*N'*-(3,4-dichlorophenyl)urea; *N*-(2-carbomethoxy-5-*tert*-butyl-3-pyrrolyl)-*N'*-(1-naphthyl)urea; *N*-(2-carbomethoxy-5-*tert*-butyl-3-pyrrolyl)-*N'*-(2-naphthyl)urea; *N*-(2-carbomethoxy-5-*tert*-butyl-3-pyrrolyl)-*N'*-(3-chloro-4-fluorophenyl)urea; *N*-(2-carbomethoxy-5-*tert*-butyl-3-pyrrolyl)-*N'*-(3-chloro-4-methylphenyl)urea; *N*-(2-methylcarbamoyl-5-*tert*-butyl-3-pyrrolyl)-*N'*-(2,3-dichlorophenyl)urea; *N*-(2-methylcarbamoyl-5-*tert*-butyl-3-pyrrolyl)-*N'*-(1-naphthyl)urea; *N*-(*N*-methyl-2-carbomethoxy-5-*tert*-butyl-3-pyrrolyl)-*N'*-(1-naphthyl)urea; *N*-(*N*-methyl-2-carbomethoxy-5-*tert*-butyl-3-pyrrolyl)-*N'*-(2,3-dichlorophenyl)urea; *N*-(*N*-methyl-2-carbomethoxy-5-*tert*-butyl-3-pyrrolyl)-*N'*-(4-methylphenyl)urea; *N*-(*N*-methyl-2-carbomethoxy-5-*tert*-butyl-3-pyrrolyl)-*N'*-(phenyl)urea; *N*-(3-carbomethoxy-5-*tert*-butyl-2-thienyl)-*N'*-(3-methylphenyl)urea; *N*-(3-carbomethoxy-5-*tert*-butyl-2-thienyl)-*N'*-(2,3-dichlorophenyl)urea; *N*-(3-carbomethoxy-5-*tert*-butyl-2-thienyl)-*N'*-(2,3-dichloro-4-hydroxyphenyl)urea; *N*-(3-carbomethoxy-5-*tert*-butyl-2-thienyl)-*N'*-(3-methoxyphenyl)urea; or *N*-(3-carbamoyl-5-*tert*-butyl-2-thienyl)-*N'*-(4-methylphenyl)urea.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/10375

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/34, 31/38, 31/40
US CL :514/423, 445, 475
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/423, 445, 475

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN
search terms: formulae within table 3 and arthritis, inflammation .

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	TARZIA, G. et al. Synthesis and antiinflammatory properties of some pyrrolo(1H,3H)[3,4]pyrimidin-2-ones and pyrrolo(1H,3H)[3,4-d] pyrimidin-2-ones and pyrrolo(1H,6H)[3,4-d]pyrimidin-2-ones. Chemical Abstracts. 27 August 1979, Abstract No. 74558p; page 594.	1-16

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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Date of the actual completion of the international search	Date of mailing of the international search report
13 AUGUST 1998	03 SEP 1998

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